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MEDICAL APPLICATIONS OF ANTI-COLIBACILLARY SERUM.*

By H. Vincent, M.D.,

PROFESSOR AT THE COLLEGE OF FRANCE,
PARIS, FRANCE.

(From the Laboratory of Infectious and Epidemic Diseases.)

Numerous works published during the last few years have directed attention to the great frequency and importance of infections due to B. coli. It has been found that a certain number of ill-defined infectious states are due to this microörganism. Primary infection of the kidney and bladder caused by B. coli is extremely common and, when slight, is apt to escape recognition.

B. coli may be the active cause of grave septicemias, particularly in children. This organ may implant itself in any of the organs or tissues: brain (H. Vincent), meninges, endocardium, pharynx, intestine (infantile cholera, severe enterocolitis), liver (intense jaundice, H. Vincent), spleen, peritoneum (gangrenous appendicitis), Fallopian tubes, ovaries, uterus, respiratory apparatus (infantile broncho-pneumonia), and the bones and periosteum (H. Vincent). It is well known as a frequent cause of infection of the urinary apparatus, the prostate and the seminal vesicles.

In nursing infants the localization of B. coli in the kidneys gives rise to extremely grave suppurative pyelonephritis, which may escape recognition simply because it has not occurred to any one to collect the urine separately. In the adult, constipation and pregnancy are frequent underlying causes of suppurative coli-bacillary pyelonephritis both acute and chronic.

B. coli is not only dangerous by reason of its infective properties and its rapid proliferation in the blood, viscera and tissues, but also

* Translated by Edgar Erskine Hume.

on account of the toxin it produces. In previous studies, I have shown that there is not merely one colibacillary toxin. The bacillus secretes (1) a neurotropic thermolabile exotoxin, destroyed by a temperature of 72° C., which causes widespread damage, sometimes indeed the destruction by true necrosis of the motor and sensory cells of the spinal cord. It also attacks the encephalon and the peripheral nerves and the sympathetic and vagus systems.

(2) Secondly there is an enterotropic thermolabile endotoxin, destroyed by a temperature of 96 to 98° C., the ill effects of which are exerted on the intestine, the mucous membrane and the intestinal glands and Peyer's patches as well as upon the hepato-biliary apparatus. There results profuse diarrhea, desquamation and congestion of the intestine, damage to the liver and catarrh of the bile ducts, etc. Colon bacilli moreover contain a toxic protein which after resisting a temperature of 100° C. is able to kill mice.

From the strictly pathologic point of view, though contrary to general opinion, there is only one species of colon bacillus. On the strength of certain morphologic, chemical and cultural characteristics (mobility, indol reaction, hemolytic properties, sugar fermentation, action on neutral red, reciprocal inter-agglutination, etc.), it had been inferred that there was an infinite number of varieties of the colon bacillus. But, as I have shown, all these varieties have one property in common, namely, that of secreting a variable quantity of exotoxin and endotoxin, the former neurotropic, the latter enterotropic and hepatotropic. The "index of toxicity" is, in accordance with a general law in microbiology, very variable according to the particular organism.

Close clinical observation of patients reveals symptoms more particularly due to one or other of the toxins or to their association. In the latter case, apart from the gastro-intestinal disturbances (diarrhea, jaundice, etc.) we may meet with more or less severe nervous manifestations such as stupor, delirium, restlessness, late paralyses, psychasthenia, mental depression, melancholia, etc. One or other of these symptoms predominates according to the case.

Experimentally we can set up choleriform symptoms in rabbits with persistent diarrhea and a low fever (endotoxin) or even nervous symptoms such as ascending paralysis, monoplegia, fantastic behavior. A rabbit injected with toxin would bite the ears of the other rabbits, both male and female, as well as guinea-pigs which had been placed in the same cage. These last-named symptoms were the effects of the neurotropic exotoxin.

As a result of my bacteriologic investigation of the colon bacillus and its toxins as well as other experimental data, I was led to prepare a therapeutic anti-colibacillary serum, at once anti-infective and anti-colibacillary, This serum, employed in numerous cases of grave colibacillosis, yielded very rapid and conclusive results.

In 1925 I published the first instances of cure by the use of this

anti-colibacillary serum. It was a case of long standing severe infection (suppurative pyelonephritis) which had proved refractory to every kind of treatment. Since that date various publications have confirmed the efficacy of this method of treatment in acute and chronic infections due to B. coli.

Medical Affections in Which Its Use is Indicated. *Colibacillary septicemia* is of rather frequent occurrence. Its symptoms closely resemble those of typhoid and paratyphoid fevers, A, B, or C, but there is no eruption of lenticular spots (H. Vincent). The diagnosis is established by blood culture. In infants it is a very fatal disease. In the adult the death rate is about 4 per cent and the disease is apt to be very protracted.

Anti-colibacillary serum treatment promptly brings about recovery from this septicemia. Under the influence of the injections of serum (20 to 40 cc. per day), the temperature almost invariably returns to normal after the second or, at latest the third, day. The stupor subsides, the tongue becomes clean, the spleen returns to its normal size, the albuminuria disappears, and the patient soon begins to ask for food.

This affection sometimes follows severe physical overstrain. I have notes of two instances of this.

Case Abstracts. CASE 1.—A young man, aged 21 years, following over-exertion in sports in the middle of summer, developed very severe protracted septicemia. Blood culture revealed the B. coli. On the 38th day of his attack the temperature was still just over 103° F. He had albuminuria with signs of myocarditis, considerable loss of weight and pronounced weakness. Then four subcutaneous injections of 20 cc. of anti-colibacillary serum, at the rate of one each day, cut short the disease. The temperature fell 36 hours after the first injection, the pulse became normal and the patient recovered without any complication or recurrence.

CASE 2.—Another instance of colibacillary septicemia of extraordinary gravity was in a girl, aged 3 years. There was hyperpyrexia of the continuous type, acute cholangitis with jaundice, intense acute nephritis with general anasarca involving the limbs, trunk, and face, complete torpor, nystagmus, clonic contractions of the face, lips and lower limbs, etc.

The prognosis pointed to imminent death. This child was given five injections (one a day) of anti-colibacillary serum with rapid, complete disappearance of all these formidable symptoms. On the third day the temperature fell to normal and the child asked frequently for food. The jaundice and edema disappeared in less than a week. The nervous symptoms cleared up after the second day. The little patient made a rapid, complete recovery.

CASE 3.—Another not less striking case was that of a woman, aged 28 years, 6 months pregnant, who was suffering from acute colibacillary septicemia with suppurative pyelonephritis, almost complete anuria, torpor, an earthy color of the skin, temperature of 105° F., jaundice, infective purpura, etc. This patient, in the wards of Professor Chevassu, appeared to be condemned to die in the course of a few days. The desirability of inducing abortion was discussed but my colleague objected, asserting that the only effect would be to kill both mother and child. The kidney pelves were drained for 24 hours and 40 cc. of the serum was injected daily for several days. The

temperature returned to normal within 36 hours. On the fourth day the patient got up and ate a mutton cutlet belonging to another patient, unknown to the doctor and nurse. She made an excellent recovery and 3 months later was delivered of a fine child, without any complication, infective or otherwise.

These instances show that we are effectually armed against the most alarming forms of the blood infection set up by B. coli.

Suppurative Pyelonephritis. This must be mentioned among the commonest localizations of colibacillosis accompanied or not by cystitis of the same kind. Of frequent occurrence in children just as in adults, often very refractory, this affection is also met with in the pregnant woman in consequence of the pressure exerted by the fetus on the right kidney and the intestine. Pressure on the renal vein further aggravates the stagnation of blood in the kidney. Whatever the cause may be, suppurative pyelonephritis yields to the anti-colibacillary serum treatment. It is as much a surgical as a medical disease. I shall deal with this in a later paper devoted to the surgical applications of anti-bacillary serotherapy.

The Gall Bladder and the Liver. Both these as I showed in 1893, are sometimes invaded by the coli bacillus in cases of grave jaundice.

CASE 4.—An elderly patient whose case was communicated to me by Dr. Verain, Chef de Laboratoire at the Nancy School of Medicine, was suffering from B. coli suppurative pyelonephritis of long standing (5 years), with cystitis and advanced anemia (1,600,000 red corpuscles). Shortly after she had a violent attack of cholecystitis accompanied by high temperature, diarrhea and grave septic symptoms. Urotropin in large intravenous doses, auto-vaccines and other forms of treatment had proved useless.

On and after October 3, 1928, this patient was given five injections (one a day) of anti-colibacillary serum. At that time her temperature was between 104 to 105° F. Within 3 days the temperature had fallen to normal. The urine became quite clear and the symptoms of acute cholecystitis had completely disappeared.

In these cases of cholecystitis we must, of course, begin by making sure that B. coli is really the cause of the condition by obtaining a specimen of bile by duodenal drainage. This bile is examined microscopically and bacteriologically and, after dilution, is inoculated in different suitable culture media for the identification and differentiation of the bacillus.

Disorders of the Nervous System. B. coli may produce nervous complications by its neurotropic toxin (exotoxin). This as a matter of fact may attack the central nervous system, the peripheral nerves or the sympathetic or vagus nerves, often setting up immediate symptoms, though these may only supervene later on. It does not always occur to us to refer such symptoms to their real causes.

Experimentally, progressive ascending paralysis consequent upon acute or chronic myelitis can be readily induced in the rabbit by the injection of colibacillary toxin. It is quite possible that some

of the cases described as Landry's ascending paralysis in man are due to intoxication produced by the neurotropic exotoxin of B. coli. Moreover, also in man, paraplegia may supervene in renal subjects (Gilbert and Lion) and in patients who have formerly suffered from colibacillary septicemia. I have seen the appearance of slow paraplegia, coming on 5 years after recovery from general infection of this kind, complicated by pyelonephritis and suppurative cystitis. The bacillus, isolated in the course of the septicemia, secreted a very active neurotoxin which rapidly paralyzed rabbits.

The clinical interest of such data is very great because they enable us to understand certain nervous affections of indeterminate origin. No doubt coli-bacilluria may and often does supervene secondarily in paraplegics, but it must be recognized that colibacillosis may itself directly determine these lesions of the spinal cord. In such case we find in experimental animals and in man, pronounced diffuse changes in the motor and sensory cells of the cord (H. Vincent, 1922).

As soon as these symptoms make their appearance, the anti-colibacillary serum should be injected forthwith because it, by virtue of its powerfully antitoxic properties (antimicrobic as well), will neutralize the toxins and bring about recovery. The administration of the serum should be continued until all the symptoms have disappeared.

Certain species of B. coli secrete extremely active neurotropic toxins.

Case 5.—An instance of this occurred in a woman, aged 70 years, who was suffering from very long standing, grave double suppurative pyelonephritis. Her urine contained a predominance of B. coli; but also staphylococci, enterococci, diphtheroid bacilli, and anaërobes.

This patient had reached an extreme degree of marasmus. She was unconscious, delirious, comatose, quadriparetic, was unable to speak or to recognize her husband and children, was suffering from fecal and urinary incontinence. Death at an early date appeared inevitable. The condition had been diagnosed uremia. In reality she had colibacillary toxi-infection.

She was given 40 cc. anti-colibacillary serum a day for 8 days, as well as my new antistreptococcal serum, in view of the presence of streptococci in the urine. This patient recovered consciousness in 3 or 4 days. The paresis of the arms and legs, the fecal and urinary incontinence, the aphasia and the mental clouding entirely disappeared. She resumed her usual life. She was able to converse, eat, telephone and look after her household, and survived for about 2 years. Colibacillary toxi-infection was therefore indubitably the cause of these grave nervous disturbances.

Cases of this kind have greatly astonished practitioners who have witnessed them. I myself, endowed with scientific skepticism, only accepted them as authentic after having directly controlled the data.

I may recall on the other hand the formidable nervous symptoms (absolute torpor, delirium, clonic and tonic convulsions of the face and limbs, nystagmus, etc.) in the child described above and who

completely recovered with extraordinary rapidity from the septicemia and from all the accompanying symptoms.

Gastro-intestinal Disorders. The study of the nervous or neuropathic symptoms present in certain cases of B. coli septicemia, as well as in certain cases of acute or long standing pyelonephritis and, lastly, in a large number of cases of refractory enteropathies (enterocolitis, chronic muco-membranous enteritis) which are neither tuberculous nor parasitic, has led me to investigate the relationship of these complications to colibacillary intoxication itself. In patients infected by B. coli, we often get more or less serious gastro-intestinal disturbances and at the same time characteristic neuropathic reactions: on the one hand, visceroptosis, ptosis of the colon, intestinal spasm, painful colic, attacks of diarrhea following periods of constipation, mucous or bilious stools, etc.; on the other hand, excessive mental irritability alternating with periods of depression, incapacity for work, melancholia, outbursts of weeping, refractory insomnia, headache, symptoms of neurasthenia or even by psychasthenia merging, it may be into suicidal tendencies.

I have brought before the Academy of Medicine of Paris* (April 19, 1930) instances of these morbid states in which the double intoxication of the patient by B. coli enterotoxin and neurotoxins were completely verified, as all the symptoms of enteritis and neuropathy disappeared in a few days after the influence of anti-colibacillary serum. And these symptoms have not recurred.

Among such cases was a woman who had been ill for 5 years.

CASE 6.—Another was that of a man, aged 72 years, who had been suffering from refractory chronic enterocolitis since 18 years of age. He had therefore been ill for 54 years. He had traveled all over Europe in search of health and had consulted numerous physicians without any other result than the confirmation of the diagnosis of a "muco-membranous enterocolitis." The various methods of treatment, and especially vaccines including autovaccine, had conspicuously failed. His neuropathic state was very bad.

Having received six injections of the anti-colibacillary serum this patient was cured in a few days. From this time forth he had regular bowel motions, no longer presented any nervous disturbances and could partake of ordinary food. The serum had given this 78-year-old man, by a striking improvement, the sense of having been restored to normal health, a feeling which he had not had since he was 18 years of age. Seven months later he stated that "his health had remained quite remarkable such as it had never been since his youth" (H. Vincent, *Academie de Médecine*, Paris, April, 29, 1930).

Nor is this characteristic case an isolated one. I have witnessed recovery in cases of much shorter standing than the preceding one but suffering nevertheless from intestinal disturbances with diarrhea and grave neuropathic symptoms, obliging them persistently to follow, without appreciable result, a very strict regimen and some-

* Vincent: Rôle de la toxi-infection colibacillaire dans certaines entéropathies chroniques. Action de la sérotherapie anticolibacillaire dans ces états morbides, Bull. Acad. de méd., Paris, 1930, **103**, 431.

times incapacitating them for work. We all know how difficult it is to bring about a cure, or even improvement, in these enteropathic neuropathic subjects.

The very rapid disappearance of this complex group of enteritic and neuropathic symptoms as soon as we had administered the specific anti-colibacillary serum, demonstrates that *the etiology and pathogeny of chronic entero-colitis, sometimes referred to as mucous or muco-membranous colitis*, must be regarded from a new angle.

It should be considered as a toxi-infectious disease, though perhaps more toxic than infectious. It is consequent upon the absorption in the small, as well as in the large, intestines of thermostable enterotoxin (endotoxin) and of thermolabile neurotoxin (exotoxin) secreted in contact with the intestinal mucosa by innumerable colon bacilli which normally vegetate in the digestive tract. This microorganism, as is well known, predominates in the intestines. We can count a hundred billion a day in the stools of the healthy subject. The enormous proliferation of this parasitic organism is inoffensive in the healthy subject, because the liver, the bile and the pancreatic and intestinal secretions are normal, and the neutralizations of the toxins is therefore continuous and complete. I have, on various occasions, repeated my researches into this physio-pathologic problem and I will sum up in a few words my views on the subject.

In the normal state the bile is the principal agent of disintoxication of the intestine. The bacteria which vegetate there in prodigious numbers and elaborate their dangerous poisons are however rendered innocuous because the bile readily and completely neutralizes their toxins as they are secreted. (H. Vincent.) The essential element of the neutralizations of the microbial poisons poured into the intestine is the normal soaps contained in the bile: the oleate, stearate and palmitate of sodium (H. Vincent, 1907). Hitherto sufficient importance has not been attached to the physiologic and biologic rôle played by these bile soaps. Yet their proportion and their fixity show that there can be no question of an indifferent principle. Analyses made by Hoppe-Seyler show that normal bile contains 1.39 per cent by weight of soaps, principally in the form of palmitate of sodium. According to Hammarsten, human bile contains 1.01 grams of fatty acid soaps per 1000. Now, as I have shown in various publications in 1907, and 1908, and 1909, since confirmed by numerous researches in other countries, especially in the United States (Larson and Nelson), these soaps have even in almost infinitesimal proportions, the property of destroying the most dangerous toxins (tetanus, diphtheria, colon bacillus, B. edematiens, septic vibrio, etc.). For instance from two to four millionths of a milligram of palmitate of sodium neutralizes an otherwise lethal dose of tetanic toxin.*

* The soaps apparently do not really destroy the toxins but are thought to envelop the particles of toxin in a film, thus transforming them into what I have termed "*cryptotoxins*." The bile salts are, strictly speaking, very slightly antitoxic.

I am inclined to think that patients suffering from chronic muco-membranous entero-colitis originally suffered from hepatic insufficiency and consequently an insufficiency, especially qualitative, of the bile secretion, the soaps not being present in their normal proportion in the bile.

In patients who are in a state of hepato-bacillary insufficiency the normal multiplication of the intestinal bacteria, more particularly of the colon bacillus, becomes a danger, the greater since these subjects are usually constipated. Furthermore as the soluble poisons secreted by these microörganisms are no longer completely neutralized by their continuous absorption, they become a continuous danger. This explains the whole of the symptoms observed in enteritic patients. The following very variable symptoms characterize such intoxications: pallor, subicteric hue or actual jaundice, tenderness of the liver or gall bladder (representing the fixation of the endotoxin on the hepato-biliary apparatus). On the other hand the spasm of the colon, colic, constipation or fetid diarrheic outbursts resulting from this spasmodic state, the contractures, either in the right or the left half of the large intestine, are the effects of the local intoxication of the vagus and the sympathetic, by the two toxins I have described. The neuropathic or constitutional troubles (asthenia, myalgia, irritability, depression sometimes giving rise to ideas of suicide, the sensation of anguish, the refractory insomnia, etc.), characterize the intoxication of the central nervous system more particularly by the neurotoxin (exotoxin) of B. coli.

I have endeavored to verify the colibacillary origin of these toxi-infectious phenomena by studies of blood reactions (the precipitative or agglutinative power of the patient's blood, fixation of the complement), but the results have been irregular and uncertain. More to the point is the finding of abundant B. coli in the urine, though this is not always the case. But in a high proportion of cases, there is one important confirmation of the elective and preponderant action exerted by the colon bacillus in producing the preceding group of symptoms and that is the rapid and often immediate disappearance of all these intestinal and neuropathic disturbances under the influence of treatment with the anti-colibacillary serum.

This new conception, at once of great theoretical and practical interest, leads to a rational understanding of the pathogenesis of an affection the nature of which is much in debate. Lastly, and most important, it culminates in the cure, hitherto very slow and very difficult, of this disease, since mucoid or muco-membranous entero-colitis may last for years, sometimes throughout life, and greatly handicap the patient's existence.

In a recent publication I called attention to the toxi-infectious, or more precisely, colibacillary origin of certain states of dementia. I have had under my care a case of a young man, aged 18 years, with dementia precox, following colibacillary septicemia. Then too

I have recorded notes of a patient, aged 47, who for 6 months had been suffering from extraordinarily obstinate constipation and ultimately from urinary colibacillosis. This patient presented symptoms of hypochondria with fugues, delirious mania, ideas of persecution and suicide, and intense mental depression and mutism. At the same time he suffered from well-marked digestive disturbances and total loss of appetite. He was cured after six injections of 40 cc. each of anti-colibacillary serum.

These examples deserve to be placed on record because they may in some cases provide an explanation, hitherto very uncertain, of various mental disturbances, and may conceivably result in their cure. In such cases, therefore, it is advisable to inoculate an animal with the urine in order to ascertain whether the B. coli be present, and systematically to investigate whether in the patients' antecedents, there have not been grave, persistent gastro-intestinal disturbances, chronic constipation, or appendicitis (a very frequent cause, as I have shown, of pyelonephritis and coli-bacillaria) or even of a septicemic infection, clinically resembling typhoid or paratyphoid fever, which may have been unrecognized colibacillemia.

It is important to commence the anti-colibacillary serum treatment in these cases as early as possible. As with diphtheritic paralyses where the fixation of the toxin in the nerve centers may become irremediable, so *pari passu* the colibacillary toxin, if the serum treatment be delayed, may cause lesions of the nerve centers which will prove refractory to this otherwise energetic treatment.

INFECTIVE ASTHMA: INDICATION OF ITS ALLERGIC NATURE.

By Robert A. Cooke, M.D.,

NEW YORK CITY.

(From the Department of Pathology and Immunology, Division of Applied Immunology, Cornell University Medical School, and the First Medical Division of the New York Hospital.)

There is no doubt but that bacterial infection of the respiratory tract may cause asthma of an acute and paroxysmal as well as of a chronic form. There is, however, a great deal of doubt whether or not asthma of infective origin should be considered as an allergic reaction. Some recent studies of this condition from two different angles may help in the solution of the problem. They deal, first, with heredity and, second, with the eosinophil response.

Heredity has been shown to be important not as a cause but as a factor that may create in the offspring of sensitized antecedents the capacity for or tendency toward that form of allergy typically

exemplified by the seasonal hay fever from pollen. The report of Vander Veer and myself,[1] in 1915, has been abundantly confirmed and accepted. In a later study by the author and Spain[2] we excluded cases not giving the immediate positive skin test. We were, therefore, dealing with that form of allergy in man characterized by a sensitization of the skin and, as a rule, by the presence of circulating antibody in the blood.

In this skin-sensitive group hereditary influences are evident, but studies on the hereditary factor in the so-called nonsensitive group of asthmatics have not appeared in the literature. With some exceptions, the terms "nonsensitive" and "infective" are practically synonymous, as applied to asthma. No immediate urticarial reaction on skin test with bacteria or their products has been found to have etiologic or diagnostic significance and, as would be expected, skin-sensitizing antibodies are not demonstrable in the blood in such cases.

We have now collected data on a series of cases of asthma that are semi-selected. By that I mean that the group comprises consecutive cases, selected only to the extent that they were studied to a satisfactory diagnosis and were cases in which an adequate family history was obtained. There resulted 688 cases. Grouped according to cause as nonsensitive (infective), sensitive (atopic) and combined, the cases are arranged, depending on the age of onset of asthma, in different age groups for comparison. The figures are tabulated in Table 1. Divided in this way some age groups are

TABLE 1.—CLASSIFICATION SHOWING HEREDITARY INFLUENCE IN THE SKIN-SENSITIVE AND THE INFECTIVE TYPE OF ASTHMA.

Asthma onset, age.	Total number cases.	Classification.						Positive antecedent history.					
		Atopic.		Infective.		Combined.		Atopic.		Infective.		Combined.	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0 to 3 . .	106	54	50	33	31	19	19	36	67	30	91	14	74
3 to 5 . .	42	25	59	7	17	10	24	16	64	6	86	8	80
5 to 10 . .	70	48	68	13	19	9	13	34	71	9	69	5	56
10 to 15 . .	55	36	65	13	24	6	11	24	67	6	46	6	100
15 to 20 . .	79	50	63	17	22	12	15	24	48	8	47	6	50
20 to 30 . .	123	70	57	39	32	14	11	31	44	14	36	6	43
30 to 40 . .	117	44	37	50	43	23	20	13	30	17	34	7	30
40 to 50 . .	54	15	28	32	59	7	13	5	33	8	25	4	57
Over 50 . .	42	7	17	31	74	4	9	0	0	8	26	1	25
Total . .	688	349	Av. 51%	235	Av. 34%	104	Av. 15%	183	Av. 52%	106	Av. 45%	57	Av. 55%

necessarily small. The high percentage (82 per cent) of positive antecedent histories of allergy in the purely infective group up to the age of 10 years, as contrasted with 67 per cent for the same age group in the skin-sensitive (atopic) cases and a positive antecedent history of allergy in 45 per cent of the entire infective group of

106 as contrasted with 52 per cent of 183 atopic cases indicates I believe, that the underlying biologic capacity for sensitization transmitted to the offspring by allergic antecedents is similar in the infective and the atopic cases.

We are not here so much interested in the fact that in 195 cases of asthma the antecedent history was one of asthma in 66 per cent and of other atopies in 34 per cent. This is somewhat lower than the 80 per cent obtained by Clarke, Donnally and Coca.[3] It seems important, however, that in a specially studied small group of 66 infective asthmas the antecedent history was one of pollen hay fever in 29 per cent. How many of the remaining 71 per cent had antecedents whose reaction was to noninfective causes could not be accurately determined, but there were a number. *Vice versa* not infrequently we find in atopic asthma an antecedent asthma of infective origin. We have not been able to study directly antecedent and descendant asthmatics in sufficient number for statistical figures, but the facts stated indicate not merely a similarity but rather an identity of the transmitted biologic factor in nonsensitive and sensitive asthmatics.

The second angle from which we may derive some light on the possible allergic nature of infective asthma is obtained by a study of the eosinophil cells in asthmatics of the sensitive and nonsensitive types. The difficulties of such a study are enhanced by the lack of knowledge and agreement among hematologists on such points as the origin and function of this cell in normal and pathologic states and the source and nature of the acidophilic granules. I shall only summarize from the very extensive literature on the subject the points dealing with questions of immediate interest. Of the monographs on eosinophilia those of Downey[4] and Ringoen[5] are most useful on account of the careful and critical survey of preceding literature as well as their own contributions.

Normally the eosinophils of the blood may be formed in the bone marrow by a homoplastic, *i. e.*, a mitotic, form of development, but more largely they are believed to develop by a heteroplastic differentiation from nongranular mononuclear marrow cells and, in some mammals, in the hemolymph nodes. Ringoen[5] states (p. 36): "Many eosinophil leukocytes are developed in the hemolymph nodes, for numerous mononuclear forms are present."

As to the nature and origin of the acidophilic granules of the cells there is great diversity of opinion. That the granules are exogenous material taken up by phagocytosis is maintained by Weidenreich and Schott, Sabin, Gutig, Bodertscher, Lewis and others,* while Maximow,* Downey[4] and Ringoen[5] seem clearly to have shown that at least as far as normal bone marrow is concerned the granules are an endogenous differentiation of the cytoplasm of nongranular cells and in their earlier stages may be basophilic.

* Quoted from Downey: Loc. cit., pp. 153 and 194.

An extramedullary or histogenous origin of eosinophil cells has been observed under certain experimental conditions, which we now recognize as those that produce a hypersensitive state. This view is supported by Weidenreich, Maximow, Downey, Gutig, Pappenheim and Dominici. Such a development was first observed by Weidenreich following repeated intraperitoneal injections of red blood cells, and he supposed the eosinophil granules in cells of the taches laiteuses of the rabbit omentum were hemoglobin phagocytosed by lymphocytes. This erythrocytic origin of the granules had been disproved by Maximow, Sternberg, Downey and particularly by Ringoen in his monograph in 1922.

In 1912 Schlect and Schwenker[6] studied eosinophils in anaphylaxis. These authors noted a marked blood eosinophilia in guinea pigs after shock and showed eosinophilic infiltration of lung and peribronchial tissues, peritoneal fluid and tissue fluid from areas of skin edema (Arthus phenomenon). They believed that the eosinophil cells were drawn to the tissues from the blood and marrow and were not formed at the site of reaction.

Ringoen's more recent work (1922) substantiates the findings of these authors. He agrees that the eosinophil cells in peritoneal fluid produced by repeated intraperitoneal injections are not locally produced, chiefly because of the associated blood eosinophilia. He did find an histogenous tissue eosinophilia after a single subcutaneous injection of hemoglobin. Tissue from an injected site was examined from the third to the twelfth day and mononuclear eosinophil cells, which he believes to be clasmatocytes, were found. He states further (p. 55): "A résumé of the literature . . . . shows that a number of authors have derived eosinophilic leukocytes from various sources. Lymphocytes, large mononuclear, plasma cells and adventitial cells have all been taken into account as the parent cell of tissue eosinophils." Thayer,[7] in 1897, and Brown,[8] in 1898, showed the presence of eosinophils in muscle tissue infected with trichinæ. They believe the neutrophils were transformed in the reaction, but most hematologists do not agree with this conclusion.

Schilling[9] gives 3 per cent as the normal for eosinophils in the blood of man. An eosinophil increase is seen in man in metazoan infestations, eczema, asthma, anaphylactic shock and serum disease and, as Hickling[10] has shown, it may be a postinfective phenomenon. It also occurs in scarlet fever and during the third week of liver feeding in pernicious anemia.[11]

In asthma the presence of a blood eosinophilia has long been known, but it is so inconstant and irregular that no significance can be attached to it. It is certainly more apt to be present when blood is examined during the attack. In an article by the writer,[12] in 1918, 90 cases were reported. The eosinophil count was above 4 per cent in 68 per cent of the cases with positive skin tests and in 47 per cent of those with negative test.

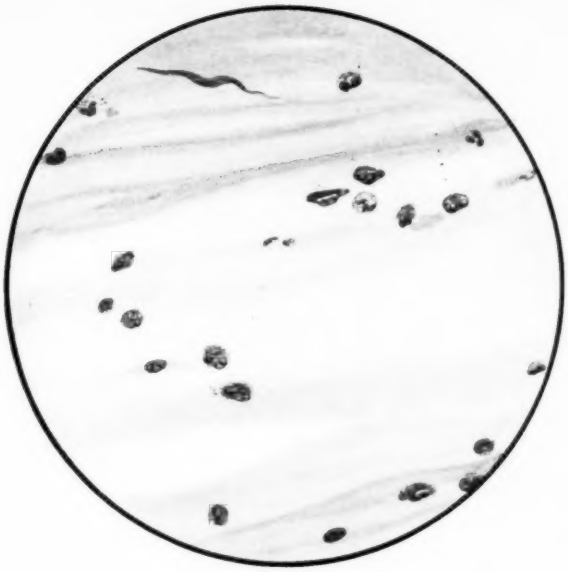

FIG. 1—Nasal washings.

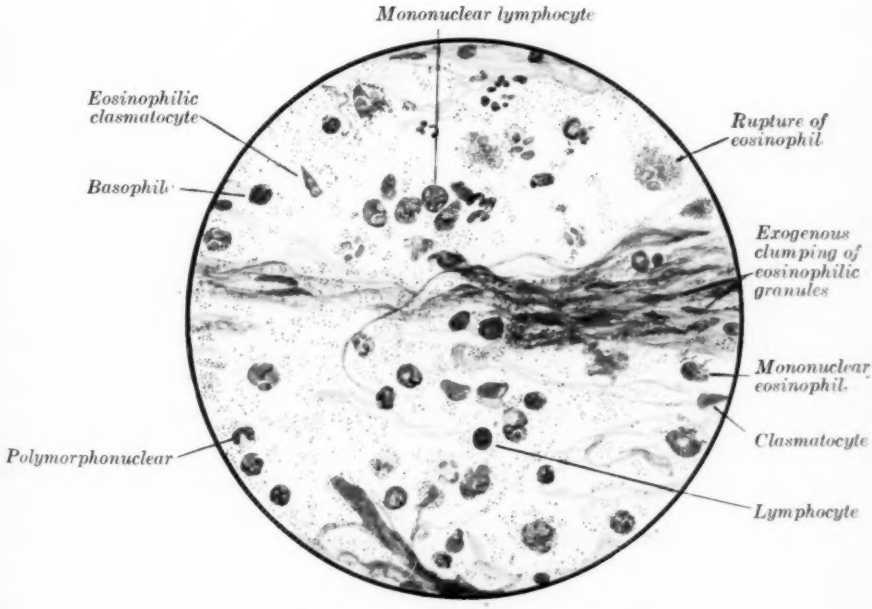

FIG. 2.—Sputum. Blood showed 4% eosinophils.

Marked eosinophilic infiltration of the bronchi has been described in most of the pathologic reports on asthma since Huber and Koessler's[13] noteworthy contribution in 1922. In view of the fact that at autopsy many eosinophil cells are seen in the bronchial wall, it can scarcely be questioned that these cells in the sputum are derived from the tissues of the bronchi directly. During asthmatic attacks eosinophil cells may be found in the sputum in practically all cases with repeated examinations, according to our previous studies.

A similar type of eosinophilic infiltration is also well known in the so-called hyperplastic or hypertrophic forms of rhinitis and sinusitis with or without polypi. In a recent paper Coates and Ersner[14] report on examinations of the antral membrane in 50 cases, as follows: "The cellular elements in the tissues were: Round-cell infiltration, lymphocytes, polymorphonuclear leukocytes and occasional eosinophils in the nonasthmatic group. The asthmatic membrane presented a predominance of eosinophils with some polymorphonuclear leukocytes and lymphocytes."

Kountz and Alexander[15] examined the nasal mucous membrane in 1 of their cases dying of asthma and found many eosinophil cells. Hansel[16] has recently reviewed over 1000 cases studied by him in which nasal and sinus pathology existed in allergic individuals, and he notes the almost constant presence of eosinophil cells in such tissue. Just as has been noted for sputum, eosinophil cells are abundant in the nasal and particularly the antral discharge. Eyerman[17] reported these cells in 72 per cent of a hypersensitive group and in 9 per cent of the nonsensitive group.

In practically all of these reports one is led to infer, or else the statement is made, that this eosinophilia of tissues and secretions of bronchi and sinuses is an allergic reaction and, therefore, cannot be due to the bacterial infection alone. In fact Hansel says in his sixth conclusion: "The part played by bacteria as etiologic factors in nasal allergy has not been proved, and the general consensus of opinion is that bacteria are secondary invaders." Huber and Koessler,[13] discussing the eosinophil infiltration of bronchi in asthma, say: "Its constant absence in certain forms of bacterial asthma is regarded as one important piece of evidence that there are types of asthma that may not be of allergic origin." To this point of view we take exception and will give reasons for believing that the eosinophil cell represents an allergic reaction of tissue to bacteria or their products.

Since our earlier report,[12] in 1918, we have been increasingly impressed by the presence of blood eosinophilia in asthma of purely infective origin, and during the past few months have collected data*

* I am greatly indebted to my associate, Dr. R. C. Grove, for his diagnosis on the nasal condition of these patients and to Miss Winifred Kelly, whose special training in hematology has provided unusual technical assistance.

which while not extensive will bear presentation now. The cases have been carefully studied, tested and classified as shown in Table 2. The groups as arranged are self-explanatory. In Groups

TABLE 2.—EOSINOPHIL STUDY ON 131 ACTIVE CASES.

Group.	Blood.		Sputum.		Sinus discharge.		No. with eosinophils low in blood, but abundant in sputum and sinus discharge.
	No. exam.	No. over 5%	No. exam.	No. with eos. abundant.	No. exam.	No. with eos. abundant.	
I. Asthma: infective only	31	19*	13	13	16	13	7
II. Asthma: infective (also other allergens)	13	8	...	...	...	...	3
III. Asthma: infective and atopic	32	24	...	...	...	...	1
IV. Asthma: atopic	18	8†	1	1	...	...	1
V. Coryza: infective allergy	15	7	...	...	10	6	3
VI. Urticaria	13	1	...	...	...	...	
VII. Chronic sinus infection	9	0	9	1	9	0	

* 9 above 8%; maximum, 27%. † 1 above 8%; maximum, 9.5%.

I and II infection is the sole cause of asthma, but it was thought that infection in cases with other allergies of the skin-sensitive type (Group II), such as pollen hay fever, though not active at the time of examination, might yield higher results than the purely infective asthmas (Group I). This does not seem to be the case. We find that a blood eosinophilia is not only more frequent but it is also on the average higher in infective asthma than in the asthma caused by substances to which a positive cutaneous test was obtained (Group IV).

That the eosinophils of sputum and antral exudates are probably of local tissue origin and not myelogenous is indicated: (1) By the fact that 15 cases in Groups I to V, with normal differential counts of the peripheral blood, showed abundant eosinophil cells in the secretion or exudate of bronchial and nasal mucous membranes; (2) a careful study of such smears also indicates that the eosinophil cells of the exudates are not all morphologically similar to those of the blood taken at the same time.

The eosinophilic leukocytes of the blood are typical polymorphonuclear cells, while the eosin-staining cells of the exudates are not only polymorphonuclear but often more largely mononuclear, resembling both lymphoid cells and reticuloendothelial cells.

Reproductions of characteristic slides showing these findings were made from smears of antral and bronchial secretion in a boy, aged 13 years (No. 3466), with an acute upper respiratory infection and associated asthma. His blood showed 4 per cent eosinophils. This was his first attack of asthma since tonsils and adenoids were removed 5 years before.

In many cases the eosinophil granules are abundant throughout

the smears of the exudates and do not appear to have the grouping that is characteristic of ruptured eosinophil cells. This indicates that the acidophilic granules are formed outside the cells and are later ingested by all cells with phagocytic capacities, and under these conditions are strictly exogenous. This agrees with Downey's statement (p. 154) of Weidenreich's material which he examined: "All possible intermediate stages lead from the free granules to the fully differentiated eosinophil leukocyte."

In experimental anaphylactic shock eosinophil cells represent some phase of the allergic reaction, and since this reaction is a systemic one, medullary stimulation ensues with resulting blood eosinophilia.

We may hypothesize then that in asthma and in hay fever of the skin-sensitive type, blood eosinophilia results only when the allergic reaction is sufficiently general and systemic to affect the bone marrow. Sternberg[18] has shown that during active hay fever eosinophilia generally, though not invariably, occurs, and Cohen, Ecker, Breitbart and Rudolph[19] proved that pollen may be absorbed from the nasal mucosa into the circulatory blood and so effect a systemic bone-marrow response.

So in infection, whether it be scarlet fever, empyema or asthma, the eosinophil production which may result may be regarded as a sensitization phenomenon equally as well as it is so regarded in serum disease and experimental anaphylaxis. When the infection is localized, as in the sinuses, an allergic reaction to bacteria may result, with subsequent formation of eosinophil cells in the infected tissues and thence in their secretions, but this only occurs in those individuals capable of such sensitization. For example, in chronic suppurative sinus infection without asthma it is rarely found in the discharge or in the blood. Only one of our 9 cases showed an excess in the sputum, in none was there an increase in the blood, and antral pus showed none.

In infective asthma secondary to sinus disease an excess of eosinophil cells in the sputum and antral discharge is practically a constant finding, whereas an increase in the blood is found in but 61 per cent, and in our series, in Groups I and II, 10 cases with normal blood eosinophil content showed excess of eosinophil cells in the sputum and antral discharge. The opposite condition of increased blood eosinophilia with absence of eosinophil cells in sputum and antrum has not been observed by us in infective asthma secondary to sinus disease.

These facts lead us to believe that in this condition the eosinophil production is a local histogenous one and represents a local bacterial allergic reaction. If the particular stimulus is sufficiently absorbed to affect the bone marrow a blood eosinophilia would secondarily result. By such an hypothesis only can we explain the greater frequency of eosinophil cells in nasal and bronchial membrane and

secretion than in the blood. Support to this view is given by the fact that the histogenous eosinophil cells are not all morphologically like those of the blood, hence the theory that they are drawn to the tissues from the blood is not tenable, nor does such a surmise explain the presence of free acidophilic granules in the sputum and nasal discharge.

Very little has heretofore come of the study of eosinophilia, though its relation to asthma has long been known. The present study contributes at least one fact that I believe of basic importance, namely, that an eosinophilia, local or general, is as important a part of the cellular response in asthma of infective origin as in asthma of the skin-sensitive type. It is an immunologic, or, more specifically, an allergic response comparable to precipitin, agglutinin or other antibody.

Summary. 1. Asthma of infective origin appears to be subject to hereditary influence. This, of course, only proves that asthma, whether of the infective or skin-sensitive type, is the offspring of hereditary influences. But the facts that 15 per cent of all asthmas are combined sensitization and infective types, that skin-sensitive allergies are frequent in the antecedents of infective asthma and that the opposite condition also obtains, all lend support to the view that both types may be regarded as of the same nature.

2. Eosinophilia may be regarded as an allergic phenomenon. Experimentally it is produced only under conditions which are regarded as favoring sensitization. Local eosinophilia of histogenous origin is believed to be shown. Eosinophilia is as frequent in asthma of infective origin as in that of the skin-sensitive type.

3. Infective asthma may be regarded as an allergic reaction quite as properly as is the skin-sensitive type, although the immunologic reactions in the two forms are not identical.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*†

I. Two New Methods for Direct and Indirect Observation.

By Pol. N. Coryllos, M.D.,
PROFESSOR OF CLINICAL SURGERY AND RESEARCH ASSOCIATE IN SURGERY,
AND
George L. Birnbaum, M.D.,
RESEARCH ASSISTANT IN SURGERY,
NEW YORK.

(From the Department of Surgical Research, Cornell University Medical College.)

In recent papers we have endeavored to stress the importance of bronchial obstruction in various types of lung pathology. Fundamental researches on the relation of bronchial obstruction to pulmonary disease were done as far back as 1844 and 1846 by Mendelssohn[1] and Traube,[2] who obstructed the bronchi of animals with shot, paper and gum arabic and produced atelectasis. It remained, however, for Lichtheim,[3] in 1879, to show that ligation of a bronchus is followed by absorption of the gases of the air and atelectasis, but that a combined ligature of the bronchus to a lobe and its corresponding pulmonary artery is not followed by atelectasis. This was the first definite demonstration that the blood circulation through the lung is an indispensable factor concerned with the absorption of gases in the alveoli. Moreover, under direct vision he observed the actual speeds of absorption of carbon dioxid, oxygen and nitrogen by the lung. The objection could be raised, and not without

* This work was aided by a gift of Mrs. John L. Given in support of Surgical Research and a grant from the National Research Council Fund.

† A complete bibliography will accompany the third and last paper of this series, "A Theory of Atelectasis."

justification, that some of the observations of Lichtheim are non-physiologic in the sense that the thoracic cavity had been opened during the course of the experiments.

We shall not attempt to discuss here the train of thought by which bronchial obstruction has been correlated with atelectasis, post-operative pneumonia, lobar pneumonia and other pathologic states of the lung. In our previous papers[4,5,6,7,8,9,10] we endeavored to give a comprehensive history and view of the subject in general and of the special importance of bronchial obstruction in the pathogenesis of pulmonary disease.

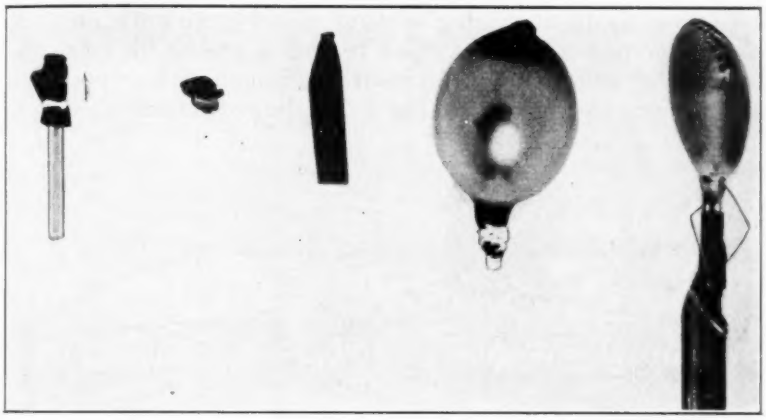
More particularly controversy has waxed keen concerning the etiology of postoperative atelectasis. We believe it may conservatively be stated that at the present writing the only definitely proven direct etiologic factor in its production is complete bronchial obstruction. We shall show in this series that in complete bronchial obstruction, by the normal play of gas exchanges a complete absorption of gases from the alveoli and atelectasis ensue. This concept will be elaborated in the second and third papers of this series, entitled, respectively, "The Behavior and Absorption Times of Oxygen, Carbon Dioxid, Nitrogen, Hydrogen, Helium, Ethylene, Nitrous Oxid, Ethyl Chlorid and Ether in the Lung" and "A Theory of Air Absorption in Atelectasis."

During the course of our studies we developed a technique for following closely under direct vision the gas exchanges within the lungs from the time of complete bronchial obstruction to the completion of atelectasis. The methods to be described have been unusually valuable in giving us an insight into the finer mechanism of the production of atelectasis and the exchange of various gases through the pulmonary endothelium. In addition, they offer an excellent opportunity for further studies on the lung, be it from the standpoint of the thoracic surgeon, the anesthetist, the internist or the physiologist.

We shall describe below the indirect, or "closed-chest" technique, and the direct, or "open-chest" technique. With both methods complete bronchial obstruction is obtained by a special type of cannula through which gas samples may be drawn from below the obstructed portion of the lung. With the first method the pulmonary changes are followed by Roentgen ray and fluoroscopy, the chest being intact. By the second technique the chest is wide open, allowing direct observation of the lungs through an "oscillating negative pressure box" which closely simulates the physiologic condition of a closed thorax. In the second and third papers of this series, to follow, we shall describe the results and theoretical and practical conclusions arrived at with the aid of these methods, described below.

Technique. In previous papers we showed that atelectasis can be constantly produced experimentally if a bronchus is obstructed in

an air-tight manner. For this purpose we elaborated a specially constructed one-way valve elastic balloon, which was introduced by the bronchoscope into a chosen bronchus of the dog. This balloon (Fig. 1), described elsewhere,[10] can be inflated from the outside and then detached from its connection and left in place. Ten to 15 hours later roentgenographic examination of the animal, placed on a special stand for obtaining symmetrical pictures, shows the characteristic pictures of atelectasis with the displacement of the heart, the trachea and the diaphragm to the affected side and opacity of the affected lung. We believe that if we were able to produce atelectasis regularly it was because we used as an obstructive agent an elastic balloon and not a solid plug of cork, wood or



1 *2* *3* *4* *5*

FIG. 1.—The balloon used for the obstruction of a bronchus in an air-tight manner. *1*, A glass tube, 4 cm. long and a little less than 0.5 cm. across. Over its distal end a piece of old rubber glove, about 2 by 3 cm., has been placed with a double lateral twist and tied. A one-way valve in the direction of the arrow is thus formed. *2*, End or head-on view of the valve, showing the lateral twists of the rubber in the formation of the valve. *3*, A piece of rubber Kollman tubing, about 4 cm. long, into which the glass and valve are introduced. *4*, The rubber tubing has been tied in an air-tight manner around the glass tube, 1 cm. from its proximal end, "E," and air has been inflated at this end which is open. The balloon is over-inflated to show the perfectly competent valve shimmering through the transparent balloon. *5*, The completed balloon, which has an outer protecting cover of organic material, is depicted as having been previously introduced into the desired bronchus in the deflated state. It is now blown and ready to be detached and left in the bronchus. The reader should refer to *Archives of Surgery* (1928, **16**, 528) for exact details.

metal, such as that tried by others before and after our investigations. We are convinced that with solid bodies it is almost impossible completely to obstruct a bronchus which yields and the diameter of which changes constantly with expiration and inspiration.

The solution of our present problem, however, required a new technique. We had to devise an instrument that would enable us to obstruct a bronchus completely, through the bronchoscope—in order to avoid opening of the chest or trachea. We must also be

able to draw alveolar air from below the obstruction for determination of gas percentages and intrapulmonary pressure. After a number of trials we constructed two types of apparatus, which gave us full satisfaction.

Intrabronchial Cannulas. The first apparatus is composed of two thin-walled brass tubes of 1 and 2 mm. internal diameter, respectively, and 50 cm. long. The external diameter of both tubes soldered together does not exceed 6 to 7 mm., so that the instrument easily passes through Jackson's full lumen 9-mm. bronchoscope. The narrow tube terminates 15 mm. proximal to the larger one, which is longer and has around its free end a wire crown to avoid obstruction by bronchial mucosa. For the same reason small lateral openings are made around this end. Above and below the distal opening of the small tube two brass rings are soldered around it, each of them bearing a groove for tying the small rubber balloon. Several models with more or less important modifications were made. In Fig. 2 *1'–1* shows a bronchial catheter

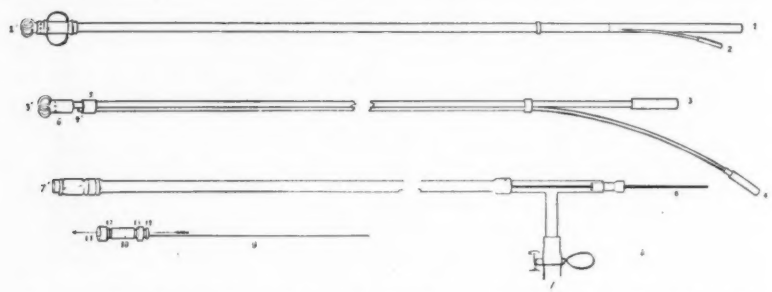


FIG. 2.—Intrabronchial catheters of Coryllos and Birnbaum. Model *1–1'* is composed of a large external metal tube (5 mm. in diameter) which terminates in a free end surrounded by a crown (*1'*) in order to avoid closure of this end by bronchial mucosa. A smaller tube passes into this tube and emerges 15 mm. from its distal end (*1'*), where it is soldered, so that there is no connection between Tubes 1 and 2. Around the distal end of the small tube is tied a piece of Kollman rubber tube, so that when air or fluid is introduced through *2* the rubber is distended, forming an obstructing balloon, as outlined. *3–3'* is the model described in the text, showing *3–3'*, the larger bronchial tube, and *4–4'*, the smaller one, which serves for the inflation of the obstructing balloon which is not depicted in the diagram. *7–8* is the latest model; it is more detailed but is not essentially different from the preceding ones.

in which the small brass tube passes inside the larger tube throughout its length and emerges near its distal end, where it is filed down level with the outside tube, to which it is carefully soldered. Models 7 and 11 are the latest modification. A piece of fine India rubber tube (the tubing used for Kollman's urethral dilator is excellent) is put over the distal end of the cannula and securely tied around the groove with fine silk thread. This rubber tube is inflated through the small metal tube after the instrument is introduced into the chosen bronchus and forms an obstructing balloon. The

accurate inflation of the balloon is one of the most important points of the technique. It must be sufficient to obstruct the bronchus completely but not so excessive as to interfere with the circulation or innervation of the bronchus or with the ventilation of the other bronchi by displacement of the interbronchial spur or carina. These requirements are imperative, since, as a rule, these experiments last for many hours. It is necessary to know at all times whether the degree of inflation and obstruction remains unchanged. For this reason we devised a closed mercury manometer system

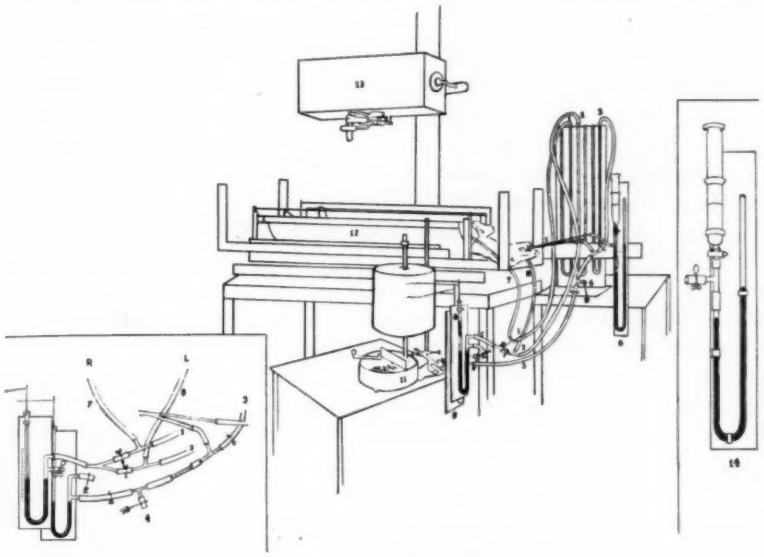


FIG. 3.—Lay-out of closed chest experiment. The animal is placed on our special Roentgen ray stand (*12*) and the bronchus blocked by means of the intrabronchial catheter (*5*) connected to the mercury manometer (*6*) (enclosure *14*), which allows checking up its degree of inflation. In each pleural cavity a cannula is placed connected to rubber tubes *7* and *8*. These tubes are connected (left enclosure) by *T* tubes to water manometers (*1* and *2*) and through another tube to a recording mercury manometer, so that it is possible to record on the smoked drum the tracing of the left or right pleural cavity pressure. The large bronchial tube of the bronchial catheter is connected by a *T* tube to a water manometer (*3*) and to a mercury manometer recording on the same smoked drum (*11*). A *T* tube was interposed in the latter rubber tube (*4*, left enclosure), allowing the taking of air specimens of intrapulmonary air for gas analysis. *13* is the adjustable fluoroscope or Roentgen ray unit.

(Fig. 3, *14*), the free end of which was connected by way of a *T* tube to a syringe of 30 cc. capacity. The horizontal tube was connected through a rubber tube to the small tube of the bronchial catheter. By pushing down the plunger of the syringe, already filled with water, we could inflate the balloon to a size a little greater than the estimated diameter of the bronchus on which bronchoscopy had previously been done, and a marker was placed at the height of the

mercury meniscus in the closed end of the manometer. The bronchial catheter would then be disconnected. After it was introduced through the bronchoscope into the chosen bronchus it would again be connected with the manometer and the plunger of the syringe pushed in to distend the balloon and bring the mercury meniscus slightly above the previously placed marker. As long as the mercury stood at this level we were certain that the balloon was inflated.

Two types of experiments were carried out.

I. Closed-chest Method. In the first group, which will be designated by "closed-chest method" (Fig. 3), the animal, under iso-amyl-ethyl barbituric anesthesia, was placed on the Roentgen ray stand (*12*) so that the evolution of the experiment could be watched by fluoroscopy and Roentgen ray pictures. The intrapleural pressures during the experiment were taken by two water manometers (*1*, *2*) connected with two cannulas introduced into the pleural cavities of the animal. Through the bronchoscope the pulmonary cannula was introduced and the balloon inflated, as already described. The larger tube of the bronchial catheter, which communicated with entrapped pulmonary air, was connected to a water manometer (*3*), to a recording mercury manometer and at times through a *T* tube (*4*) to the sampling bulb for analysis of specimens of alveolar air by a modified Henderson-Bailey gas analyzer. In this way it has been possible to follow simultaneously the intrapleural pressures and to record them on a smoked drum (*11*), to read and record the intrapulmonary pressure in the obstructed lung, to follow the changes in percentage of the entrapped alveolar air and to check up by fluoroscopy and roentgenographic examination the progress of atelectasis. At the same time the closed mercury manometer connected with the small tube of the intrabronchial catheter enabled us to know exactly the degree of inflation of the obstructing balloon.

II. Open-chest Method. The animal was anesthetized with sodium iso-amyl-ethyl barbiturate, 55 mg. per kilogram intraperitoneally. The neck was then shaved, the anterior wall of the chest prepared and intratracheal insufflation through the bronchoscope started. The thorax was then opened by hemisection of the sternum and a Balfour retractor was applied to maintain both thoracic cavities wide open. In the meantime (Fig. 4) a rotating valve (*8*) was connected with the suction faucet (*10*) and the number of its revolutions per minute regulated to the respiratory rate of the animal as it was before opening of the chest. The intrapleural pressure was taken before operation and the oscillations of negative pressure in the box (indicated in the water manometer, *9*) were regulated so as to be equal to the intrapleural pressure of the animal before opening of the chest. The animal was then transported to the box and its head passed rapidly through the circular

opening of it. During this short time intratracheal insufflation was discontinued without any evil effect. The cover was tightly applied and the rubber collar fixed around the neck of the animal, smeared with petrolatum and secured by a gauze bandage or by a pneumatic collar, a later modification. Care was taken not to exert any unnecessary constriction around the neck. From now on the intratracheal insufflation can stop and the animal will

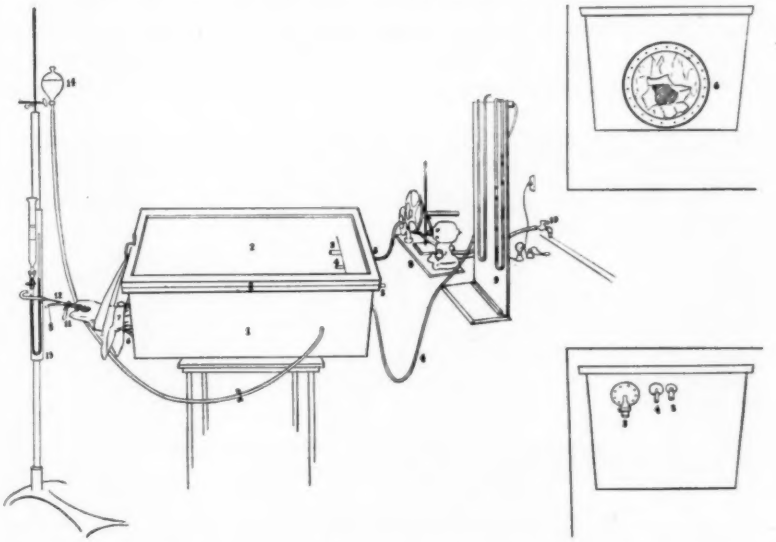


FIG. 4.—Lay-out of the open chest experiment in the oscillating vacuum box. After the chest is opened the animal is placed in the air-tight box (*1*), the cover of which (*2*) is made of plate glass. The head of the animal protrudes through the opening in the box (upper right corner enclosure *6*, and also Fig. 6), around which is fixed an inflatable rubber collar which fits snugly around the shaved and petrolatum-anointed neck of the animal. The rotating valve (*8*), interspersed between the suction apparatus (*10*) and the box inlet (*3*), insures an oscillating vacuum in the box. This pressure is measured by the water manometer (*9*) and is equal to the negative intrapleural pressure of the animal taken previous to the operation. Inlet *5* serves to regulate the pressure in the box. A rubber tube passes through one wall of the box and may be connected to a reservoir with physiologic solution of sodium chlorid; by this means fluids can be administered under the skin or into the peritoneum of the animal during the experiment. Through the bronchoscope (*11*) the bronchial cannula is introduced into the left stem bronchus, and the balloon which is to occlude the bronchus is then inflated by means of the syringe-mercury manometer arrangement described in Fig. 3. The large tube of the cannula, in communication with the entrapped intrapulmonary air, is closed off unless samples of air are to be withdrawn through it for gas analysis.

breathe with its chest wide open at the same rate and with the lungs under the same negative pressure as in the closed-chest. Moisture and temperature inside of the box were kept as near normal as possible. Fig. 5 is a photograph of the layout of the whole experiment. It has been repeatedly possible to keep the animal in fine condition in the box for from 8 to 15 hours. A small tube was

provided for, through which saline solution, cardiotonics, or additional anesthetics could be given subcutaneously, if necessary, without disturbing the experiment. The pulmonary cannula was then introduced as for the "closed-chest" method.

We wish to point out that this box is based on a different principle from the differential pressure chamber of Sauerbruch. In the latter, only one pleural cavity being open, the steady and non-oscillating differential pressure (hypo or hyper) serves to keep the lung of the opened half-chest distended while the other lung breathes normally. In our box (Fig. 5), on the contrary, both pleural cavities being widely opened, no respiration can take place unless

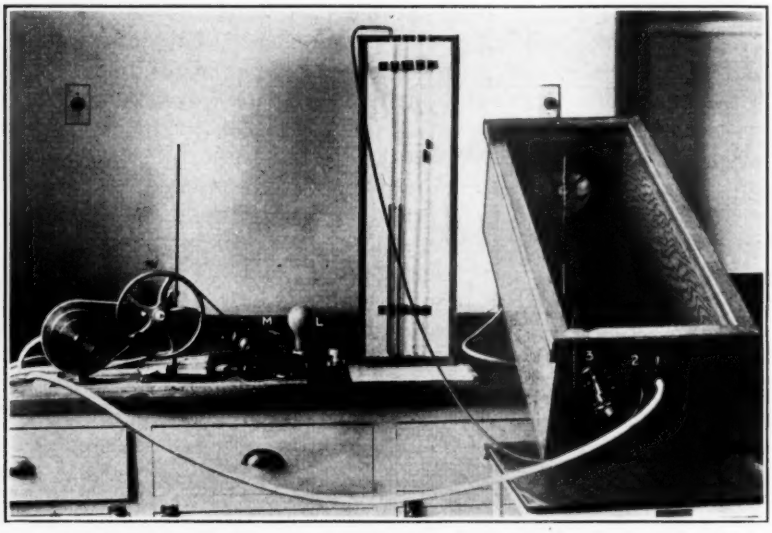


FIG. 5.—Box for oscillating vacuum. *1*, *2* and *3* are outlets corresponding to *3*, *4* and *5* of Fig. 4. *V*, rotating valve; *W*, speed-reducing wheel; *L*, 40-watt lamp resistance and *C* the cylindric collar, for the neck of the animal, which has lately been replaced by the inflatable rubber collar shown in Fig. 6.

there is an oscillation in the negative pressure box. It is in an air-tight wooden structure, measuring 33 inches (83.17 cm.) in length, 14 inches (35.48 cm.) in width and 12 inches (30.48 cm.) in height; it is covered by a glass top which runs in a groove in the frame and thus permits the box to be closed hermetically. The groove is filled with mercury or, more conveniently, with petrolatum, so that a perfect seal is obtained. The box has three outlets; two of them are 1.3 cm. in diameter and the third, 0.3 cm. The first outlet is connected with the rotating valve (*V*) which produces an oscillating vacuum. The valve is rotated slowly by a two-pulley speed-reducing mechanism, consisting of a wheel (*W*) and a motor (*M*) with a rheostat installed. An extra 40-watt lamp resistance (*L*) in the system further reduces the speed of rotation.

The valve can be regulated to perform the necessary number of revolutions a minute to make the vacuum interruptions equal to the respiratory rate before the chest was opened. The rotating valve is connected at one end with an ordinary suction apparatus or the laboratory suction faucet. The other end of the rotating valve connects directly with the box (outlet *1*). The second tube (*2*) is connected with a water manometer. The third tube (*3*), covered with a piece of rubber tubing and stopcock, connects the box with the outside air, regulating the degree of vacuum in it and allows the introduction of a thermometer. At the opposite panel of the box is a circular opening bearing a cylindrical collar (*C*) of

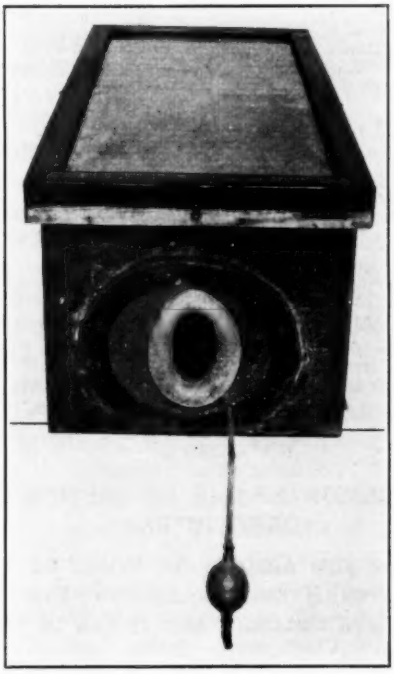


FIG. 6.—The inflatable rubber collar of the vacuum box, which fits in an air-tight manner around the previously shaved and petrolatum-anointed neck of the animal.

soft rubber tissue which can be adjusted around the shaved neck of the dog and fixed with a bandage so as to be air-tight. (More recently we have replaced this collar by a rubber collar which can be inflated with air.) (Fig. 6.)

By the methods described we have studied the absorption rates of different gases by the lung. These are described in a paper to follow. Using this technique it soon occurred to us that after the bronchial catheter was in place and a lobe of lung occluded, atelectasis could be expedited by mechanically withdrawing all the air or gas from it with a syringe and then washing out the lobe by

successively (6 or 7 times) introducing and withdrawing several hundred cubic centimeters of fresh oxygen each time, the lobe finally being left collapsed. Now the bronchial cannula is clamped off and the remnants of gases left to absorb until atelectasis occurs—a question of only minutes. "Washing out" with carbon dioxid gives an even more rapid atelectasis. The lobe is now ready for the introduction of the desired volume of gas or gases.

Summary. Two new methods are described which allow a physiologic study of the gas exchanges in a lobe or a whole lung after its bronchus has been completely obstructed.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*†

II. The Behavior and Absorption Times of Oxygen, Carbon Dioxid, Nitrogen, Hydrogen, Helium, Ethylene, Nitrous Oxid, Ethyl Chlorid, and Ether in the Lung.

With Some Observations on Pleural Absorption of Gases.

By Pol. N. Coryllos, M.D.,
PROFESSOR OF CLINICAL SURGERY AND RESEARCH ASSOCIATE IN SURGERY,
AND
George L. Birnbaum, M.D.,
RESEARCH ASSISTANT IN SURGERY,
NEW YORK.

(From the Department of Surgical Research, Cornell University Medical College.)

The phenomena of gas exchanges through a moist and living membrane such as the alveolar endothelium of the lung are quite

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† For complete bibliographies the reader should refer to the third article of this series and to previous papers of the authors.

different from those attendant upon simple physical diffusion of a gas through a porous cup. There is physical and physiologic evidence that they are dependent not only upon the speed of diffusion of a particular gas through space and its partial pressures or concentration on opposite sides of the wet semipermeable membrane but also upon its solubility and futhermore, in the lung, upon the integrity of the endothelium and of the intrapulmonary circulation. The alveolar air is separated from the venous blood by the endothelium of the air sacs and of the capillary vessels which cover their external surface and by a negligible amount of smooth and of extremely thin elastic fibers in the walls of the alveolus. Through this respiratory membrane the exchange of gases takes place.

Solubility of Gases in Fluids. When we regard the lung endothelium as a moist membrane we must consider gas exchanges as related to their solubility in it. This does not mean that the endothelium may be regarded as merely a layer of fluid, but the solubility coefficient of different gases in water gives some comparative basis upon which to formulate absorption times. Moreover, solubility of a gas is dependent upon the nature of the gas, those which are more basic or acid being more soluble than the neutral ones.* For example, carbon dioxid is much more soluble than hydrogen. The volumes of hydrogen, oxygen, carbon dioxid and nitrogen soluble in 1 cc. of water at body temperature are: Hydrogen, 0.016; oxygen, 0.024; carbon dioxid, 0.592; nitrogen, 0.016. In a mixture of gases the amount of each individual gas dissolved in a fluid is proportional to its partial pressure (Dalton's law). When a definite volume of liquid is saturated with a gas at constant temperature and pressure, an equilibrium is established between the gas in solution and that over the solution.

Diffusion of Gases Within the Alveoli and Through the Pulmonary Endothelium. With a mixture of gases in the alveoli the molecules of a particular gas diffuse through the alveolar space in all directions toward the alveolar endothelium at a rate inversely proportional to the square root of the density of the gas. The velocity of gas molecules is very great. For example, when hydrogen and oxygen are in a mixture the hydrogen molecule travels 1840 meters per second and the oxygen molecule travels 460 meters per second, for the oxygen molecule is 16 times as heavy as hydrogen ($\frac{1}{\text{square root of } 16} = \frac{1}{4}$). Alveolar air contains approximately 15 per cent oxygen and 80 per cent nitrogen under atmospheric pressure; thus 100 cc. of alveolar air would contain 15 cc. of oxygen and 80 cc. of nitrogen the mixture being under a pressure of one atmosphere. Since equal volumes of gases under the same pressures contain equal numbers of molecules, there are 80/15 as many nitrogen

* For the physicochemical aspect of the question see Getman's *Outlines of Theoretical Chemistry*, 4th ed., New York, John Wiley & Sons, 1928.

molecules as oxygen molecules in the alveolar air. It is evident, therefore, that if nitrogen and oxygen were of equal density, diffusibility and solubility in the alveolar endothelium and peri-alveolar blood, the number of molecules of nitrogen absorbed would be 80/15 as great as for oxygen. Actually we know this is not so, even though the density of nitrogen is almost equal to that of oxygen, oxygen diffusing into the blood much more rapidly than nitrogen which is only soluble to the extent of about 1 per cent in the blood. This is due to the fact that the velocity of diffusion through a moist membrane is not only inversely proportional to the square root of its density, as we have previously said, but also that it is proportional to the coefficient of solubility of the gas in the fluid concerned. That is why the speed of diffusion of carbon dioxid through a wet membrane is 30 times greater than for oxygen, although its density is greater. This can be easily shown by tying shut a frog's lung filled with oxygen or atmospheric air and placing it in an atmosphere of carbon dioxid (Loewy and Luntz). Very rapidly the lung is distended, owing to the diffusion of carbon dioxid into it, for the coefficient of solubility of carbon dioxid is 30 times greater than that of oxygen.

Oxygen and carbon dioxid are not merely dissolved in the plasma of the blood. The bulk of oxygen and carbon dioxid is in chemical combination in the blood. The first combines with hemoglobin, the second with alkali.

The Dissociation Curve of Hemoglobin in Relation to Respiration. The oxygen-hemoglobin compound has the property of dissociating with a fall in the partial pressure of oxygen; this dissociation is complete when the oxygen pressure is reduced to zero. In this way oxyhemoglobin represents an oxygen reserve in the red cells which maintains constant the amount of oxygen dissolved in the plasma, the latter representing the vapor tension of oxygen above the unstable oxygen hemoglobin compound.

Besides the partial pressure of oxygen in the alveolar air or tissues, another important factor in the dissociation of oxyhemoglobin is carbon dioxid. Increase in carbon dioxid hastens the dissociation of oxygen; it "shifts the dissociation curve of oxyhemoglobin to the right" and thus facilitates the unloading of oxygen into the tissues as the carbon dioxid in the blood increases. Although this is strictly correct, it is, according to Haldane,[2] of much less importance than the shifting of the carbon dioxid absorption curve in consequence of the reduction of hemoglobin.

In fact, decrease of oxygen in the blood and hemoglobin unsaturation increase the capacity of the blood for carbon dioxid, probably because reduced hemoglobin is a more alkaline substance than oxygen-saturated hemoglobin. The latter acting as a weak acid keeps carbon dioxid out of combination with alkali. Whatever the cause of this action may be, it is certain that saturation of hemoglobin decreases the capacity of blood for carbon dioxid, the result being that with high oxygenation the partial pressure of car-

bon dioxid in the blood rises although its percentage remains the same. For this reason more carbon dioxid is given off by the blood when its oxygen saturation is high (Werigo,[3] Bohr, Hasselbach and Krogh[4]). Now it follows that if one lung is ventilated with a neutral gas as hydrogen, and the other with air, the latter will give off nearly 50 per cent more carbon dioxid than the former. (Haldane.)

Decrease in carbon dioxid has another important result, discovered by Bohr[5] (1904) and called the "Bohr effect." Such a decrease shifts the dissociation curve of hemoglobin to the left so that whereas in the venous blood (carbon dioxid, 45 mm. of mercury; oxygen, 40 mm. of mercury) the hemoglobin is 68 per cent saturated, if carbon dioxid falls to 10 mm. of mercury the hemoglobin (without any increase in the oxygen pressure) becomes 85 per cent saturated. Furthermore, the oxygen is more firmly held in combination with hemoglobin so that notwithstanding this apparent increase in oxygen pressure and absence of cyanosis, the oxygen available to the tissues is greatly diminished.

Oxygen and carbon dioxid in the alveoli are kept quite constant at about 15 and 5 per cent, in spite of a constant interplay of gases through the alveolar endothelium. The inspiratory draft of air carries oxygen down only to a certain level in the bronchial tree; from this level oxygen, at a higher partial pressure, diffuses down through the larger and smaller bronchi and finally into the alveolar sacs where oxygen is at a lower partial pressure due to its continuous absorption from the alveoli into the blood. Similarly, on expiration, carbon dioxid is carried out of the alveoli only into the medium size bronchi, and from there it diffuses toward the larger bronchi and trachea. The mechanical carriage of oxygen and carbon dioxid in and out of the lung in the respiratory air drafts is thus a limited process, which depends upon the diffusibility of these gases to carry oxygen into the alveoli and tissues, and carbon dioxid out of the tissues and alveoli into the external air. This is, briefly, part of the intricate mechanism which, as previously stated, regulates the percentages of alveolar oxygen and carbon dioxid with such nicety.

With a lobe, containing air or other of the gases studied, cut off from the outside air by complete bronchial occlusion, the same factors we have considered in previous paragraphs come into play to bring about a complete absorption of alveolar gases (and atelectasis). The exact mechanism we leave to a succeeding paper.[6] In this paper we shall give some typical protocols, comment on the phenomena of gas exchanges when one or more gases are introduced into an occluded lobe, and summarize, as far as the present studies allow, the actual absorption times of a stated amount of gas by one lobe of the lung. For the exact technique the reader should refer to a previous paper.[7]

Changes in Entrapped Alveolar Air as Indicated by Successive Gas Analyses. The results obtained in closed as well as open chest experiments show that within 2 to 7 minutes after bronchial obstruc-

tion the oxygen percentage falls rapidly from 15 to 5 or 6 per cent. It remains at about these figures until complete disappearance of the alveolar air. (Table 1.)

TABLE 1.—CHANGES IN OXYGEN AND CARBON DIOXID PERCENTAGES AFTER OBSTRUCTION.*

Dog.	Time after obstruction.	Oxygen.	Carbon dioxid.	Comment.
466 . .	Before bronchial obstruction	14.20	4.80	
	5 min.	..	4.09	
	35 min.	2.09	4.12	Animal dyspneic and cyanotic.
	2 hrs. 50 min.	4.00	5.30	
	2 hrs. 20 min.	5.70	6.07	Animal breathes quietly.
475 . .	10 min.	3.90	6.40	
	25 min.	3.90	4.70	
	50 min.	16.70	3.09	Obstructing balloon broke.
482 . .	10 min.	6.10	6.20	
	25 min.	6.04	6.26	
	40 min.	6.57	6.49	
	55 min.	5.41	6.71	
	5 hrs. 15 min.	6.81	6.45	
	6 hrs. 15 min.	5.35	6.97	
	10 hrs. 15 min.	5.81	5.53	

* Only figures in which possibility of error in gas analysis was excluded are given in this table.

In animals in which gas analyses were performed until complete atelectasis occurred, the curves plotted for percentages of oxygen and carbon dioxid show that the percentages vary inversely. (Fig. 1.) It is thus seen that the entrapped alveolar air rapidly undergoes marked quantitative changes, the percentage of oxygen dropping and carbon dioxid rising so that their respective partial pressures tend to come into equilibrium with the corresponding gases of the venous blood. These changes occur in exactly the same way in animals as in man, as shown by Loewy and von Schroetter[8] (1905).

The succession of events as observed in the open-chest experiment, with the lung normally breathing in air, is as follows: Immediately after successful obstruction "the lung stops breathing," whereas the normal lung increases in size. There is a slight inspiratory excursion in the occluded lung owing to the decrease of pressure (increased negative pressure) in the box during inspiration, but it is insignificant as compared to the wide respiratory movements of the other lung. Little by little the size of the occluded lung decreases as a whole, without a conspicuous change in its general shape, appearance or color. Gradually it sinks toward the costovertebral sinus, whereas the other lung increases in size so that the heart is manifestly displaced toward the obstructed lung. Except for a slight cyanotic hue, the obstructed lung does not show any other

change until its volume is markedly decreased (to about one-fifth or one-seventh its original size). Then there appear dark bluish-brown patches scattered all over its surface without any predilection for the hilus or peripheral portion of the lung, as van Allen and Adams[9] reported. After the great mass of gas is absorbed atelectasis advances rapidly, and within approximately 1 hour is complete. Figs. 2 and 3 show histologic sections of atelectasis produced in open- and closed-chest experiments. Often small islands of slightly aërated light-colored parenchyma remain on the dark bluish-black atelectatic lung, the complete disappearance of which may take half an hour or more. This general picture was

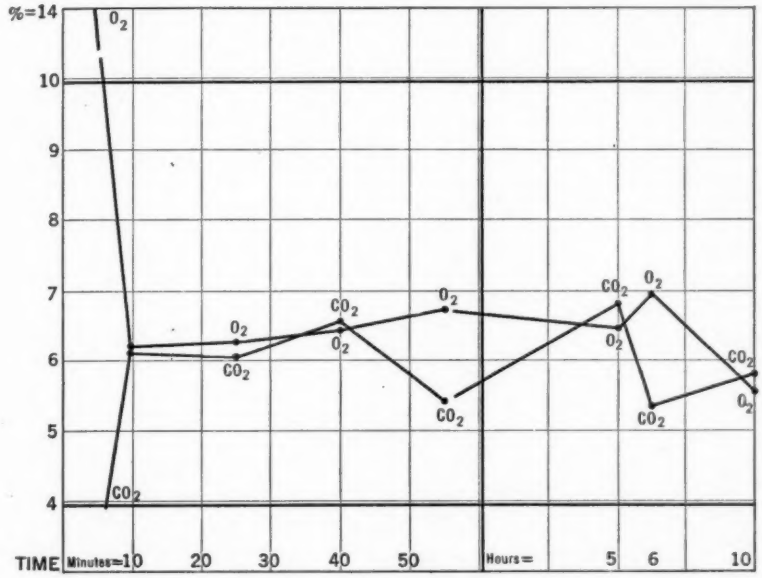

FIG. 1.—Graphic representation of percentages of oxygen and carbon dioxid obtained by alveolar gas analysis before obstruction and for a period of over 10 hours after obstruction. Dog. 482, March 30, 1930.

observed, as well, with gases other than air; only the time factor varied.

The actual volumes of gases introduced for the study of their absorption varied from 100 to 500 cc. of gas, depending for the most part upon the size of the animal. In the case of ether the pure vapor was obtained by slowly passing liquid ether through a metal coil immersed in water at 90° C., the coil in turn being directly connected to the lobe of lung under study through the pulmonary cannula. Ethyl chlorid was introduced directly in a spray from a standard commercial container through a long tube so that it reached the lung as a vapor. For the latter two vapors the volume

introduced was judged by the state of inflation of the lobe as compared to the inflation produced by measured volumes of gases previously introduced. The other gases were measured, as injected, with a P. A. Stoss-Nachfolger pneumothorax apparatus. The absorption times of a gas refer to the approximate period for absorption of gas in a lobe inflated to its full inspiratory state (for a given animal, to the same degree for each gas). It should be noted that the volumes of gas and their "absorption times" are given and not the "absorption rate." The actual "absorption rates" would have to be given in terms of cubic centimeters of gas per minute per square centimeter of absorbing surface of the lung at the particular time; this would be very difficult because the circulation and the area of the absorbing surface of a lobe are variable factors depending upon the particular state of inflation of the lung at any one moment. There are two opposing factors which normally regulate absorption. As the lung shrinks down the alveolar capillary circulation becomes progressively poorer as we have shown elsewhere,[10] but the relative absorbing surface becomes greater per unit volume of contained gas, since the volume of an alveolus decreases relatively much more than its surface. (Fig. 4.)

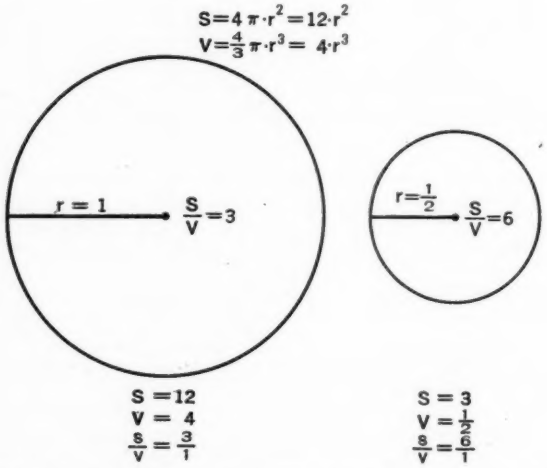

FIG. 4.—Showing the mathematic acceleration in absorption rate of gases in the alveoli of the lung. These relations probably hold true up to a point where the capillary circulation is definitely impaired.

Absorption of Oxygen and Carbon Dioxid. Closed-chest experiment. Dog 489. The experiment lasted 9½ hours.

May 5, 1930. 11.45 P.M.: The rubber balloon on the cannula was introduced into the right lower bronchus.

11.52 P.M.: The balloon was blown up with 3 cc. of water.

11.54 P.M.: A sample of gas was obtained from the obstructed lung, 15 cc.; it contained 5.85 per cent carbon dioxid and 9.05 per cent oxygen.

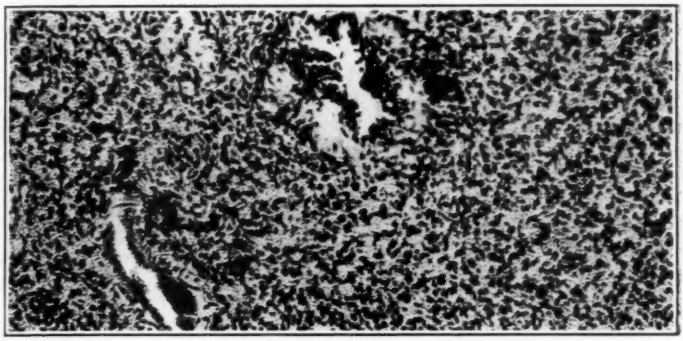

FIG. 2.—Photomicrograph showing atelectasis produced in the open-chest experiment.

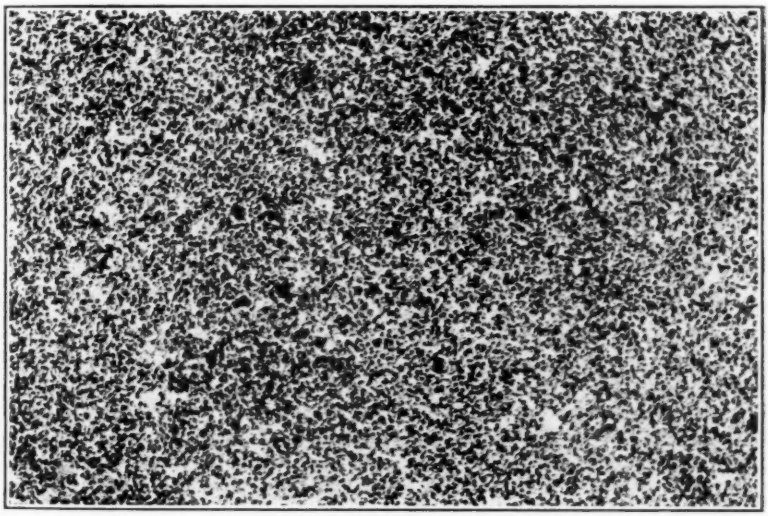

FIG. 3.—Photomicrograph showing atelectasis produced in the closed-chest experiment.

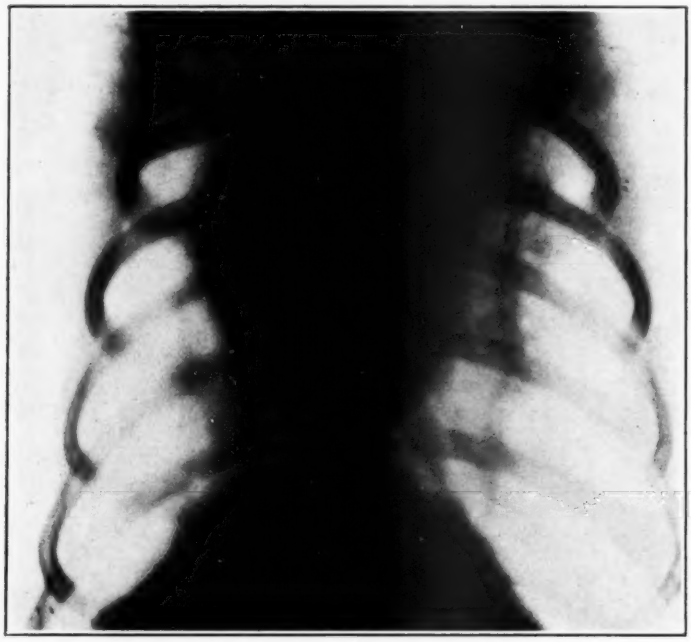

FIG. 5*A*

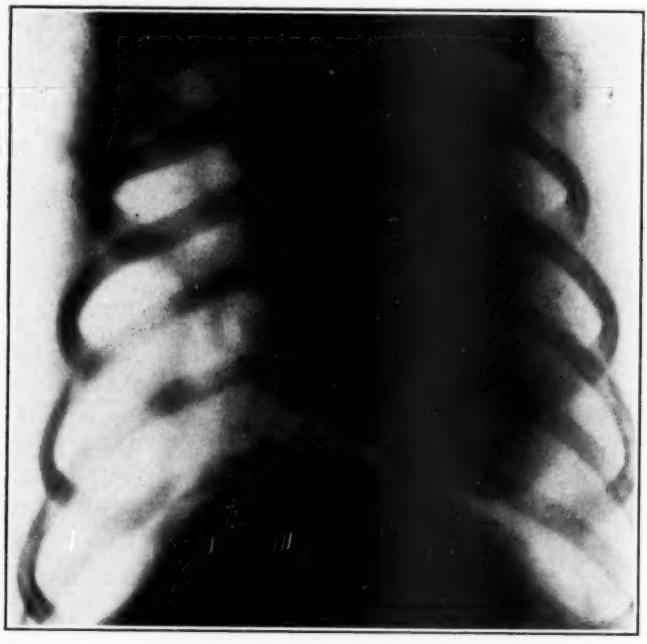

FIG. 5*B*

FIG 5.—Dog 511. *A* was taken after the introduction of 290 cc. CO_2 into the left lower lobe which appears distended. *B* was taken 10 minutes after the introduction of CO_2 into the left lower lobe. The gas has been completely absorbed.

FIG. 6.—Interstitial hemorrhage and edema in the left lower lobe after introduction of 100 per cent ether vapor into the lung previously rendered atelectatic (open chest experiment).

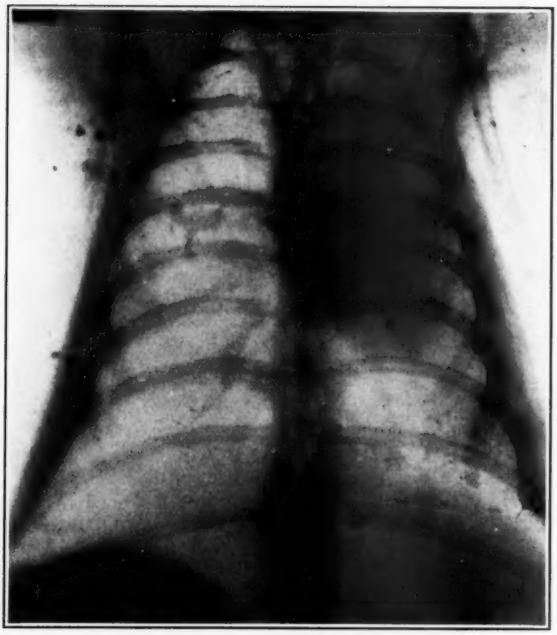

FIG. 7*A*

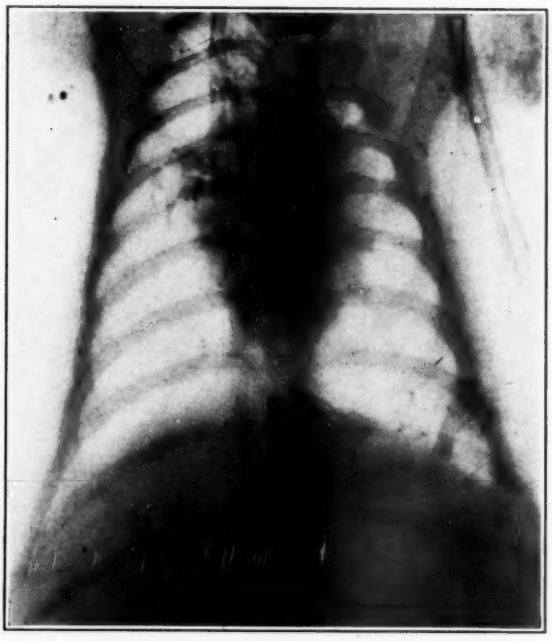

FIG. 7*B*

FIG. 7.—*A*, roentgenogram of a rabbit's chest after introduction of 75 cc. oxygen into the right pleural cavity. *B*, after complete absorption of gas from the pleura cavity; the heart has returned to its normal position.

12.03 A.M.: A sample of gas contained 5.98 per cent carbon dioxid and 6.66 per cent oxygen.

12.17 A.M.: A sample of gas contained 5.9 per cent carbon dioxid and 6.43 per cent oxygen.

12.28 A.M.: A sample of gas contained 6.1 per cent carbon dioxid and 7.36 per cent oxygen.

12.41 A.M.: A sample of gas contained 6.07 per cent carbon dioxid and 6.15 per cent oxygen.

12.52 A.M.: A sample of gas contained 6.05 per cent carbon dioxid and 6.02 per cent oxygen.

1.21 A.M.: Only 2 cc. of gas could be obtained.

1.35 A.M.: A roentgenogram showed a definite shift of the heart to the right.

1.53 A.M.: 100 cc. of oxygen was introduced into the obstructed lung. Roentgenograms taken 1 and 2 minutes later showed the heart shifted to the left.

1.58 A.M.: A sample of gas from the obstructed lung contained 6.94 per cent carbon dioxid and 51.2 per cent oxygen.

2.10 A.M.: A roentgenogram showed the heart again back to the right side.

2.15 A.M.: Only 4 cc. of gas could be obtained; this amount was insufficient for analysis.

2.22 A.M.: Fluoroscopy showed the heart a little more to the right than before the administration of oxygen. The respiration was very quiet.

3.50 A.M.: Fluoroscopy showed increased density of the right lower lobe.

5.26 A.M.: 100 cc. of carbon dioxid was introduced into the obstructed lung.

5.26½ A.M.: The heart was shifted to the left; the right lower lobe was clear.

5.30 A.M.: Only 4.8 cc. of gas could be obtained. It contained 54.16 per cent carbon dioxid.

5.32 A.M.: A roentgenogram showed the heart back again on the right; the breathing was very quiet.

6.25 A.M.: Fluoroscopy showed no further change; the right side of the diaphram was immobile, and the heart moved toward the right on inspiration. There was no ventilation in the obstructed lung.

9.15 A.M.: A roentgenogram showed no change. The animal was sacrificed with 30 cc. saturated solution of magnesium sulphate injected intravenously.

9.20 A.M.: Autopsy revealed atelectasis of the right lower and accessory lobes (confirmed by microscopic sections). (See Figs. 5A and 5B, Dog 511.)

Open-chest experiment. Dog. 498, 10 kg. The experiment lasted 14 hours; negative pressure was −4, −7.5 of water; oscillation rate, 14 per minute; temperature in the box, 40° C.

May 15, 1930. 11.35 A.M.: The left lung was obstructed.

1.07 P.M.: A sample of gas contained 6.09 per cent carbon dioxid and 4.74 per cent oxygen.

8.30 P.M.: Atelectasis was complete in 9 hours.*

10.40 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.

10.50 P.M.: A sample of gas contained 8.59 per cent carbon dioxid; the oxygen percentage was beyond the limit of the apparatus.

* In these experiments we were able to know with certainty when atelectasis was complete by the characteristic dark bluish color of the lung; this was repeatedly verified by histologic sections.

11.00 P.M.: The left lower lobe was again atelectatic; all the gas was absorbed.
11.10 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.
11.20 P.M.: The left lower lobe was again atelectatic; all gas was absorbed.
11.25 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.
11.31 P.M.: The left lower lobe was much smaller; 100 cc. more of oxygen was introduced.
11.35 P.M.: A sample of gas contained 10.63 per cent carbon dioxid; the oxygen percentage was beyond the limit of the apparatus.
12.13 A.M.: 100 cc. of carbon dioxid was introduced to distend the left lower lobe.
12.14½ A.M.: All the carbon dioxid was absorbed; the lobe was again atelectatic.
12.16 A.M.: 100 cc. of oxygen was introduced to distend the left lower lobe again.
12.27 A.M.: The oxygen was completely absorbed; the lower left lobe was again atelectatic.
12.37 A.M.: 50 cc. of oxygen and 50 cc. of carbon dioxid was introduced to distend the lower left lobe.
12.41 A.M.: All the gas was absorbed; the lobe was again atelectatic.
1.02 A.M.: 150 cc. of 100 per cent ether vapor was introduced to distend the lower lobe.
1.03 A.M.: All the ether was absorbed; the lobe was atelectatic again.
1.09 A.M.: 100 cc. of nitrogen was introduced into the left lower lobe.
1.25 A.M.: The heart stopped beating; the lung was unchanged.

Summary. The absorption time for oxygen in this experiment averaged 15 minutes; for carbon dioxid, 1.5 minutes; for 100 per cent ether vapor, 1 minute.

TABLE 2.—ABSORPTION TIMES OF OXYGEN AND CARBON DIOXID INDIVIDUALLY INTRODUCED IN A LUNG PREVIOUSLY RENDERED ATELECTATIC.

Dog.	Oxygen.		Carbon dioxid.		Comment.
	Cc.	Absorption time, min.	Cc.	Absorption time, min.	
511 . .	150	15	290	5	Closed chest experiment; roentgenographic control; other gases besides oxygen and carbon dioxid were successively introduced.
	275	15	275	5	
	280	12	250	7	
507 . .	..	....	100	2½	Open-chest experiment.
504 . .	..	....	100	2	Open-chest experiment.
498 . .	100	10 and 11	100	1½	Open-chest experiment.
499 . .	275	13	300	3	Open-chest experiment.

The figures in Table 2 show that the absorption times of oxygen and carbon dioxid show a constancy which is in agreement with the physical laws of diffusion and solubility. These times, however, seem to vary according to the anatomic conditions of the alveolar endothelium. This supposition is made on the bases of findings in Dog 504, in the atelectatic lungs of which were successively intro-

duced in the following order: nitrous oxid, carbon dioxid, ethyl chlorid, ethylene, carbon dioxid, ethyl chlorid, carbon dioxid, ethylene, oxygen and ether vapor. Because of the lesions of pulmonary endothelium by the gases introduced in it, carbon dioxid at the first introduction was absorbed in 2 minutes; at the second introduction, in 21 minutes, and at the third introduction, in 1 hour and 22 minutes.

Nitrogen when introduced alone under atmospheric pressure into the atelectatic lung was absorbed within 16 hours in Dog. 517. When pure nitrogen or other neutral gases, as hydrogen or helium, are introduced into an atelectatic lung, gas analysis of the alveolar content shortly thereafter shows that oxygen and carbon dioxid are present in the same percentage as in the alveolar blood, that is, about 5 or 6 per cent each. At the same time under fluoroscopic examination we found that after introduction of nitrogen there is at first a slight expansion of the lung which could be explained as due to the more rapid diffusion of oxygen and carbon dioxid from the venous blood into the alveoli than of nitrogen into the blood. From these facts it can be deduced, that when after the introduction of pure nitrogen the oxygen and carbon dioxid have reached these figures the absorption of the alveolar gases from this point on should proceed at the same rate as if air were now present.

Results Following Introduction of Neutral Gases Separately into the Atelectatic Lung. Nitrogen, hydrogen and helium were the gases used in these experiments.

Dog 517. Closed-chest experiment. This animal weighed 11 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used and the left lower lobe bronchus obstructed.

5.30 P.M.: The left lower lobe was atelectatic.

5.45 P.M.: 100 cc. of nitrogen was introduced.

9.35 P.M.: A specimen of gas contained 5.51 per cent oxygen and 7.34 per cent carbon dioxid.

9.40 A.M. (next day): The lung was again atelectatic, showing that *the nitrogen was completely absorbed in 16 hours.*

Dog 515. Closed-chest experiment. This dog weighed 12.5 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used. The left bronchus was obstructed.

12.10 P.M.: The left lung was rendered atelectatic.

12.40 P.M.: 105 cc. of hydrogen was introduced.

4.30 P.M.: A specimen of alveolar air contained 6.16 per cent oxygen and 5.03 per cent carbon dioxid.

9.57 P.M.: A specimen of alveolar air contained 5.50 per cent oxygen and 6.38 per cent carbon dioxid.

6.00 A.M. (next day): Lung again atelectatic, showing that the absorption time for hydrogen was 18 hours.

Dog 510. Closed-chest experiment. This dog weighed 22 kg. Sodium iso-amyl-ethyl barbituric anesthesia was given. The left stem bronchus was obstructed.

8.30 A.M.: Atelectasis was complete. 175 cc. of pure helium was introduced into the left lung.

9.30 A.M.: Gas analysis showed 5.83 per cent oxygen and 9.34 per cent carbon dioxid.

1.00 P.M.: Gas analysis showed 5.34 per cent oxygen and 6.22 per cent carbon dioxid.

2.10 P.M.: Gas analysis showed 5.25 per cent oxygen and 6.64 per cent carbon dioxid.

4.30 P.M. (next day): Lung almost but not completely atelectatic in 26 hours.

TABLE 3.—EXCHANGE OF ALVEOLAR GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF VARIOUS GASES INTO AN OBSTRUCTED LOBE OF THE LUNG.

Gas.	Dog.	1930, May.	Description.	Time.	CO_2, per cent.	O_2, per cent.
Helium	507	22	Open-chest experiment; left lower lobe washed out 9 times with oxygen and allowed to become atelectatic; 150 cc. of helium was introduced into it at	2.00 P.M.		
				2.10 P.M.	4.54	2.66*
				5.45 P.M.	5.03	2.83*
Helium oxygen	510	23	Closed-chest experiment; left lower lobe was obstructed and allowed to become completely atelectatic; 200 cc. of a mixture of equal volumes of helium and oxygen was then introduced into it at . .	5.50 P.M.		
				8.00 P.M.	5.86	8.29
Helium	..	..	This lobe was now washed out 3 times with pure helium and 175 cc. of helium was introduced into it at	8.30 P.M.		
				9.30 P.M.	9.34	5.83
			The next day at	1.00 A.M.	6.22	5.34
				2.10 A.M.	6.64	5.25
Hydrogen	515	27	Closed-chest experiment; left lower lobe was washed out 7 times with oxygen and allowed to become atelectatic; then 105 cc. of hydrogen was introduced into it at .	12.40 P.M.		
				4.30 P.M.	5.03	6.16
				9.57 P.M.	6.38	5.50
Nitrogen	517	27	Closed-chest experiment; left lower lobe was obstructed and washed out 3 times with nitrogen by aspiration and distending it with pure nitrogen after each aspiration; then 100 cc. of nitrogen was introduced into it at	5.45 P.M.		
				9.35 P.M.	7.34	5.51

* These are unusually low figures for alveolar oxygen, probably due to poor respiration and anoxemia.

Table 3 is a résumé of these experiments.

The foregoing experiments show that a short while after the introduction of neutral gases into the atelectatic lung oxygen and

carbon dioxid diffuse through the alveolar membrane from the venous blood so that these gases are present in the alveoli under the same partial pressures as in the blood, as previously mentioned.

When a mixture of equal parts of a neutral gas and oxygen or carbon dioxid is introduced into the atelectatic lung the same phenomenon of rapid establishment of gas equilibrium occurs.

Dog 510.

5.50 P.M.: 200 cc. of equal parts of helium and oxygen by volume were introduced into the atelectatic left lung.

7.20 P.M.: Gas analysis showed 5.86 per cent oxygen and 8.29 per cent carbon dioxid.

The same modifications in the percentages of alveolar gaseous content occur when active gases (oxygen, carbon dioxid) are introduced individually into the atelectatic lung.

Dog 498. *Open-chest experiment.* This dog weighed 6.5 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used. The left bronchus was obstructed and rendered atelectatic.

10.40 P.M.: 100 cc. of oxygen was introduced into the atelectatic lower left lobe.

10.50 P.M.: Gas analysis showed 8.59 per cent oxygen and 8 per cent carbon dioxid.

If an acute pathologic alteration of the lung endothelium is produced so that the respiratory membrane loses its permeability or the capillaries are damaged atelectasis does not occur. This is shown in a remarkable way when ether in 100 per cent concentration is introduced into the atelectatic lung. Undiluted ether vapor can be rapidly absorbed (100 cc. in 1 minute), but more often it produces a hemorrhagic edema (Fig. 6) strictly limited to the obstructed portion of the lung. In these cases further introduction of gas in the lung, even of carbon dioxid, which is usually rapidly absorbed, is not followed by atelectasis. The lung has lost its functional ability for the exchange of gases through the alveolar and capillary endothelium. Production of atelectasis has become impossible. This fact is illustrated in experimental Dog 499 (open-chest), the protocol of which is given here.

Dog 499. This animal weighed 15 kg. 55 mg. of Sodium iso-amyl-ethyl barbituric per kilogram of body weight was given intraperitoneally.

April 30, 1930. 1.00 P.M.: The dog was in the oscillating negative pressure box (oscillations from −4 to −8). The oscillation rate was 14 per minute. The heart rate was 116. Temperature, 40° C. $\frac{1}{4}$ grain (16 mg.) of ephedrin sulphate was given hypodermically. The left lung was obstructed and washed out with oxygen.

4.15 P.M.: There was complete atelectasis of the entire left lung.

4.21 P.M.: Carbon dioxid was introduced to distend the left lung (about 300 cc.).

4.24 P.M.: The carbon dioxid was completely absorbed and there was total atelectasis again.

4.41 P.M.: 100 per cent ether vapor was introduced to distend the lung to the size previously obtained with carbon dioxid (ether vapor was obtained by slowly passing liquid ether through a long metallic coil immersed in water at 90° C.).

4.45 P.M.: The left lung became edematous, of a dark pink to red color and larger than the atelectatic lung was at 4.24 P.M.

4.47 P.M.: Oxygen was introduced into the left lung to distend it to its former size.

5.02 P.M.: There was no apparent absorption; the volume of the lung was the same.

5.06 P.M.: The clamp on the lung catheter was removed. A strong odor of ether came out of the catheter in a forceful stream of gas; the whole amount of oxygen introduced was withdrawn, showing that none of the oxygen and not all of the ether had been absorbed.

Postmortem. The left lung was pinkish red; in section it was very hemorrhagic and edematous. The weight of the right lung was 140 gm.; of the left (edematous) lung, 232 gm. Microscopic section showed interstitial hemorrhage and edema.

Table 4 shows absorption times of ether in 2 experiments.

TABLE 4.—ETHER ABSORPTION TIMES.

Animal.	Weight, kg.	Volume, ether vapor.	Absorption time, min.
498	10	150	1
504	12	200	3

It is seen that 100 per cent ether vapor is quickly absorbed by the lung in each case, but often after the first introduction and always after a subsequent one it rapidly produces a hemorrhagic edema of the obstructed lobe, so that the lobe in question has lost its functional ability to absorb any gas or vapor which may be introduced into it from now on.

Tables 5 and 6 are summaries of a closed and open chest experiment, using various gases successively in a lower lobe.

TABLE 5.—ANIMAL 511. CLOSED-CHEST EXPERIMENT.

Gas.	Volume.	Absorption time, min.
Nitrous oxid	280	23
Oxygen	275	15
Ethylene	250	25
Oxygen	280	14
Carbon dioxid	275	5
Ethylene	275	15
Oxygen	275	12
Carbon dioxid	250	3
Nitrous oxid	250	17
Nitrous oxid	250	22

It will be noted that the absorption times in the open-chest run higher than for the closed-chest. This is probably due to the fact that fluoroscopic observation through the chest is not delicate enough to allow detection of the end point of absorption; that is,

after the great bulk of gas is absorbed further shrinkage of the lung and absorption of the minimal remnants cannot be followed by fluoroscope. (Figs. 3, 5*A* and 5*B*.) In the open-chest experiment absorption of the last traces of gas can be observed directly.

TABLE 6.—ANIMAL 504. OPEN-CHEST EXPERIMENT.

Gas.	Volume.	Absorption time, min.
Nitrous oxid	175	35
Carbon dioxid	175	17
Ethyl chlorid	175	10
Ethylene	175	29
Carbon dioxid	200	21
Ethyl chlorid	500	17
Carbon dioxid	300	42
Ethylene	300	13
Oxygen	300	19
Ether	200	3

From Table 5 it might appear that nitrous oxid and ethylene are innocuous to the pulmonary endothelium; even with repeated introduction their absorption times as well as those of oxygen and carbon dioxid are not prolonged. It should be remarked, however, that with nitrous oxid 5 cc. of serous fluid was obtained from the lobe of lung 11 minutes after its introduction and 1 cc. of serous fluid 22 minutes after its introduction. With ethylene 24 cc. of serous fluid could be withdrawn from lung 1½ hours after introduction of the gas. This probably indicates the irritating effect of one or both gases. After the second introduction of ethylene 10 cc. of gas could still be withdrawn 2½ hours after its introduction and yet fluoroscopy showed the appearance of the lung to be the same as at 15 minutes after introduction. It would appear then, that the great mass of ethylene (and also nitrous oxid) is absorbed quite readily, but that later with the lung almost atelectatic the absorption process is much slower, possibly due, for one thing, to a combination of impoverishment of capillary circulation in the collapsed state and, on the other hand, to a slight degree of endothelial damage. Considering the figures of the table, and that 100 per cent concentration of gases were used, it is likely that nitrous oxid and ethylene in concentrations usually used in anesthesia are fairly innocuous to the lung. The experiments cited for 100 per cent concentration of ether vapor show it to be much more irritating, hemorrhagic edema, as a rule, being produced, so that high concentrations of ether in anesthesia are to be particularly avoided. From Table 5 we saw that even assuming very slight endothelial damage, the successive absorption times for the great mass of gases were not materially lengthened by nitrous oxid and ethylene introduction. In Table 6 the first carbon dioxid introduction after the first nitrous oxid introduction was followed by atelectasis in 17 minutes, as compared to 3 to 5 minutes for carbon dioxid in Table 5. We

should probably deduce from Table 6 that nitrous oxid introduction was the cause of the lengthening of the carbon dioxid absorption time. However, Table 5 does show that *successive* introductions of ethylene and nitrous oxid did not prolong the absorption times of gases subsequently introduced. In Table 6 it is seen that the absorption times for carbon dioxid at successive introductions were relatively increased, being 17, 21 and 42 minutes respectively. Since the new factor introduced in Table 6 is ethyl chlorid, this may point to the deleterious effect of 100 per cent concentration of ethyl chlorid vapor on the endothelium. This effect does not appear to be permanent, for the larger second volume of ethylene following ethyl chlorid took only 29 minutes to absorb; later, ethylene following the second ethyl chlorid introduction took only 13 minutes, possibly because of the beneficial effect of the intervening carbon dioxid introduction. That the ethyl chlorid effect is not permanent is shown by the fact that the final oxygen introduced took only 19 minutes to absorb, about the average normal period. On the contrary, the ether vapor effect appears to be permanent.

TABLE 7.—AVERAGES OF ABSORPTION TIMES OF GASES FROM A LUNG INFLATED TO FULL INSPIRATORY STATE.

Oxygen	15 min.	Nitrous oxid	17 to 35 min.
Carbon dioxid	4 "	Ethylene	13 to 29 "
Nitrogen	16 hrs.	Ethyl chlorid	10 to 17 "
Hydrogen	18 "	Ether	1 to 3 "
Helium, over	26 "		

For the sake of completeness, it is of interest to compare the absorption times of air, nitrogen, oxygen, carbon dioxid, hydrogen and helium in the pleural cavity, with those for the lung; for the pleura is a closed cavity completely lined with an endothelial membrane, permeable to gases, over half of which is in close relation to the capillary system of the lung. Therefore, it would not be surprising if gas absorption in the pleural cavity were accomplished according to the same laws which regulate gas absorption in an alveolus completely closed off by bronchial obstruction. This conception which will be elaborated in a forthcoming paper on gas behavior in the human pleura justifies the presentation of the data to follow.

Behavior of Gases in the Pleural Cavity. Some preliminary observations were carried out in rabbits, rather than the dog, for they have a mediastinum which is much more comparable to that in the human. The mediastinum of the dog is a flimsy structure which is permeable to gases and fluids so that a unilateral pneumothorax is not possible. On the contrary, in rabbits a measured volume of gas can be introduced into the pleural cavity of one side and unilateral pneumothorax produced. Its absorption is followed by observing the degree of return of the heart and mediastinum

back to their normal position as checked up by fluoroscopy and Roentgen ray. (Figs. 7*A* and 7*B*.)

The gases used were air, nitrogen, oxygen, carbon dioxid, hydrogen and helium. In each case 75 cc. were introduced into the pleural cavity of a rabbit weighing about 2 kg., and the absorption times studied by fluoroscopy and Roentgen ray. (Table 8.) This volume of gas produced a very marked shift of the heart to the opposite side. (Figs. 7*A* and 7*B*.) In 3 experiments carbon dioxid, oxygen and nitrogen were introduced into the pleura and samples of gas later removed for analysis of their carbon dioxid and oxygen contents. In this way some insight into the nature of gas exchanges through the pleura was to be had.

TABLE 8.—ABSORPTION TIMES OF GASES INTRODUCED INTO THE PLEURAL CAVITY OF RABBITS.

Gas.	June, 1930.	Rabbit.	Volume gas introduced, cc.	Pleural cavity.	Absorption time.
Air	4	18	75	Right	6 days
Nitrogen	4	14	75	Right	6 "
	16	16	75	Right	6 "
Oxygen	11	16	75	Left	2 hrs.* for 40 cc.
Carbon dioxid	11	14	75	Left	5 min.
Hydrogen	4	17	75	Right	4 days
Helium	4	16	75	Right	4 "
"	16	14	75	Right	4 "

* 35 cc. of gas were withdrawn for determination of carbon dioxid and oxygen percentages.

TABLE 9.—TRANSPLEURAL EXCHANGE OF GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF VARIOUS GASES INTO THE PLEURAL CAVITY OF RABBITS.

Gas.	Rabbit	Date.	Description.	Time.	CO_2, per cent.	O_2, per cent.	N_2, per cent (by subtraction).
Carbon dioxid	19	May 1, 1931	75 cc. carbon dioxid in right pleural cavity at	11.00 A.M.			
			Gas sample at	11.06 A.M.	90.00	1.50	8.50
Oxygen	16	May 11, 1930	75 cc. oxygen in left pleural cavity at	2.40 P.M.			
			Gas sample at	3.00 P.M.	6.53	93.40	Trace
			Gas sample at	4.40 P.M.	6.52	93.44	Trace
Nitrogen	18	June 11, 1930	75 cc. nitrogen in left pleural cavity at	3.55 P.M.			
			Gas sample at	4.15 P.M.	4.67	3.67	91.66
			Gas sample next day at	8.30 P.M.	5.69	9.90	84.41

Table 8 is a summary of pleural absorption times. In the pleura, as in the lung, the times of absorption for the inert gases, nitrogen,

hydrogen, helium, and for air are relatively high, as in the lung, oxygen and carbon dioxid have comparatively short absorption times.

TABLE 10.—TRANSPLEURAL EXCHANGE OF GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF CARBON DIOXID INTO THE PLEURAL CAVITY OF THE DOG.

Gas.	Dog.	Date.	Description.	Time after introduction.	CO_2 per cent.	O, per cent.	N, per cent (by subtraction).
Carbon dioxid	671	May 9, 1931	250 cc. CO_2 introduced into right pleural cavity at . .	11.50 A.M.			
				3 min.	96.00	1.5	2.5
				15 min.	69.4	10.2	20.4
				1 hr., 7 min.	10.9	15.2	73.9
				2 hrs., 20 min.	6.4	14.1	79.5

TABLE 11.—SUMMARY OF SOLUBILITY COEFFICIENTS AND ABSORPTION TIMES OF VARIOUS GASES.

Gas.	Density, gm. per 1000 cc.	Molecular weight.	Solub., gm. per 100 gm. H_2O.	Temp.	Solub. coeff., cc. gas sol. in 1 cc. H_2O.	Absorption time.	
						Pleura* (rabbit).	Lung† (dog).
Air	1.30	..	0.004	35° C.	0.015	6 days	16 hrs.
Nitrogen . . .	1.25	28	0.003	35° C.	0.012	6 days	16 hrs.
Oxygen . . .	1.43	32	0.007	35° C.	0.024	2 hrs.	15 min.
Carbon dioxid .	1.98	44	0.330	35° C.	0.592	5 min.	4 "
Hydrogen . . .	0.09	2	0.00025	35° C.	0.016	4 days	18 hrs.
Helium . . .	0.18	4	0.00020	25° C.	0.014	4 "	26 "
Nitrous oxid . .	1.95	44.20	0.067‡	37° C.	0.326	..	17 to 35 min.
Ethylene . . .	1.27	28.03	0.010‡	37° C.	0.080	..	13 to 29 "
Ethyl chlorid vapor	2.86	64.50	0.878§	37° C.	3.07	..	10 to 17 "
Ether vapor . .	3.11	74	4.962§	37° C.	15.94	..	1 to 3 "

* 75 cc. of gas introduced into pleural cavity.
† Enough gas to inflate one lobe to full inspiratory state.
‡ Volumetrically determined by us with the eudiometer.
§ Gravimetrically determined by us.

Gas Exchanges in the Pleura. In Table 9 the pleural gas exchanges following introduction of carbon dioxid, oxygen and nitrogen in the pleura of rabbits are given. When carbon dioxid was introduced into the pleura gas analysis 6 minutes later showed that 1.5 per cent O_2 and 8.5 per cent N_2 had diffused into the pleural cavity. Due to the very rapid absorption of CO_2 in the rabbit, analysis of the pleural gases over an appreciable period was found impossible. For this reason 250 cc. of CO_2 was introduced into the right pleural cavity of a dog weighing 10 kg. (Table 10.) Owing to the flimsy mediastinum of the dog, which is permeable to gases, a bilateral pneumothorax was thus produced, and 20-cc. samples of pleural gas were withdrawn for analysis over a period of 2 hours

and 20 minutes after introduction of carbon dioxid. Two hours and 45 minutes after introduction 55 cc. of gas could still be withdrawn from the right pleural cavity. Table 10 shows a progressive fall in CO_2 percentage and rise in O_2 and N_2 percentages, the last reading showing 6.4 per cent CO_2, 14.1 per cent O_2 and 79.5 per cent N_2, or approximately the composition of alveolar air or of the gases in arterial blood. We are as yet unable to state definitely the relative importance of the visceral and parietal pleura in the pleural exchange and final equilibrium of gases. This phase of the subject is still under investigation.

When oxygen was introduced into the pleura, analysis 20 minutes later showed a carbon dioxid percentage of 6.53 and an oxygen percentage of 93.4. Gas analysis 1 hour and 40 minutes later showed practically the same percentages. Carbon dioxid had therefore diffused into the pleural cavity and was present at about venous blood concentration. (Table 9.) Only traces of nitrogen had diffused into the pleural cavity. An equilibrium thus tended to be established; a perfect equilibrium is never obtainable so long as the absorbing power of the pleura is unimpaired. The constant imbalance and continuously changing partial pressures of gases or vapors on opposite sides of an absorbing membrane can account for this lack of equilibrium. Aside from this factor, in considering the rapidity of absorption and diffusion of gases through living membranes or tissues, an analogy is to be found *in vitro* in the diffusion of gases from one side of a membrane and through it into a stream of running water rather than into a beaker of water. A fresh stream of blood, arriving as it does in a relatively unsaturated state, is available to dissolve and continuously to carry away gases or vapors from the pleura or lung.

When nitrogen was introduced there was a diffusion of nitrogen out of, and oxygen and carbon dioxid into the pleural cavity. Gas analysis 20 minutes after the introduction of nitrogen showed that 4.67 per cent of carbon dioxid and 3.67 per cent oxygen had diffused into the pleural cavity. These percentages were obviously below equilibrium points because gas analyses 28 hours later showed carbon dioxid had risen to 5.69 and oxygen to 9.9. The latter figure for oxygen, which is between the venous oxygen concentration (5 per cent) and arterial concentration (14 per cent), may indicate that a further rise of oxygen percentage would have been found in subsequent analyses, or else that oxygen in the pleura now tended to be in equilibrium with arterial blood.

Pleural Absorption Compared to Pulmonary Absorption. From Table 11 it will be noted that in the pleura, as well as in the lung, air, nitrogen, hydrogen and helium require a long period for absorption compared to oxygen and carbon dioxid; for the former gases are dependent chiefly on their degree of solubility in the moist endothelium and blood for absorption from the lung. That the

density, and therefore diffusibility, has very little to do with the time of absorption of an inert gas, is clearly demonstrated in the case of nitrogen and hydrogen which are about equally soluble in water. Nitrogen with a molecular weight of 28 is 14 times as dense as hydrogen with a molecular weight of 2. Nitrogen, therefore, has only about 0.26 $\left(\frac{1}{\sqrt{14}}\right)$ the diffusion speed of hydrogen and should, theoretically, require 4 times as long to absorb as does hydrogen; yet in the pleura nitrogen required only 1.5 times as long a period to absorb as did the hydrogen. In the lung, nitrogen and hydrogen were absorbed in approximately equal times. Although the solubility coefficients of oxygen and carbon dioxid are respectively 2 times and 50 times that of nitrogen (Tables 8 and 10), the former two gases were absorbed from the lung and pleura in far less than one-half and one-fiftieth the time for nitrogen. As previously mentioned in the case of oxygen and carbon dioxid, the factors of affinity of carbon dioxid for alkalies of the tissues and blood and of oxygen for hemoglobin account for rapid absorption of these gases as compared with nitrogen, hydrogen, helium and air. These factors appear to obtain both for the pleural cavity and the lung. Carbon dioxid is apparently quite as rapidly absorbed from the pleura as from the lung. Oxygen would appear to be slower in absorption from the pleura, and the inert gases, nitrogen, hydrogen, helium and air require considerably longer times for pleural absorption.

It would not, however, appear surprising for the pulmonary absorption of a gas to be more rapid than pleural absorption; in fact, it is rather to be expected. The construction of the lung is ideal for gas absorption, the myriads of alveoli offering a large absorbing surface (a maximum of 1000 square meters) for the gases contained within them. Each alveolus is surrounded by a rich capillary network in intimate contact with the very thin pulmonary endothelium through which a rapid interchange of gases can take place. As compared with the pulmonary endothelium the pleura offers a relatively small absorbing surface for the volume of gas introduced into the pleural cavity; it is not endowed with a highly specialized capillary network such as is found around each alveolus. It seems reasonable to deduce, therefore, that the most of the absorption is carried out by the visceral pleura, notwithstanding the lung's decrease in surface and the impaired circulation due to collapse of the underlying pulmonary tissue. This may be why the rate increases as the lung expands (improved pulmonary alveolar circulation) and decreases as the pleura thickens. On this important point studies on the human are being carried out at Metropolitan Hospital, Tuberculous Service, New York City.

In a general way Table 11 shows that both for gases and anesthetic vapors the absorption times for the lung are inversely proportional to the solubility coefficients of the gases and vapors studied. This

is shown by taking the solubility coefficient of nitrogen, an inert gas, as a standard, and comparing to it the solubility coefficient of the gas or vapor in question, remembering that the higher the solubility coefficient, the quicker is the absorption. Oxygen and even the highly soluble carbon dioxid are noticeable exceptions to the rule. The affinity of carbon dioxid for alkali of the tissues and blood and of oxygen for hemoglobin, already pointed out, account for the relatively rapid absorption of these gases from the pleural cavity and lung.

Ethylene required a much shorter time for absorption and ethyl chlorid vapor and helium a little longer time for absorption than calculated from the water solubility coefficients of these gases. Ether vapor was absorbed most rapidly of all, as would be expected from its high solubility coefficient, in spite of the fact that its diffusibility is least of all the vapors and gases studied (because of its high density); its absorption time is in agreement with the findings of Van Mechelen,[11] who showed ether to be absorbed from the human lung with great rapidity. He found that on inhalation of 1½ liters of air containing from 9 to 26 per cent ether (26 to 78 gm. per 100 liters air) over 95 per cent of the ether was absorbed from the human lung in 2 seconds. Van Mechelen found that ether was in some instances considerably less soluble in blood than in distilled water. However, there are two other factors aside from the high solubility of ether which can account for the rapid absorption of ether from the lung. The first is that arterial blood (carotid artery) in a single and first passage through a lung containing about 14 per cent ether became two-thirds saturated with this anesthetic. The second point is that Van Mechelen showed the arterial blood to contain considerably more ether than the venous blood even after more than 3 hours of anesthesia. The venous blood thus remains relatively unsaturated by ether for long periods and so can absorb considerable volumes of ether vapor as it courses through the lung again and again. In the light of these considerations the rapid absorption of ether from the lung becomes clear.

A point of interest is the cause and mechanism of the possible irritant or even corrosive action of strong concentrations of ether vapor in the lung. As previously stated, 100 per cent concentration ether vapor often produced hemorrhagic edema of the lung in our experimental animals. A possible contributory cause of this may lie in the fact, as we have found, that ether containing traces of water may exist as a liquid at body temperature (37° C.), whereas pure ether boils at 34.5° C. and can exist only as a vapor at body temperature. Moreover when water is dissolved in ether to the extent of 9.92 to 100 gm. of ether (0.09 gm. H_2O per gm. ether) a perfect solution is obtained, which does not boil below 45° C. Due to water vapor in the lung and water in the endothelium itself, it is conceivable, therefore, in view of what we have just said, that

ether in high concentrations in the lung may condense and remain as a liquid on the pulmonary endothelium. Such liquid ether might irritate pulmonary tissue first by its dehydration of the endothelium and then by a direct action upon it. This could account for the hemorrhagic edema produced by high concentrations of ether vapor in the lung.

Summary and Conclusions. Gases and anesthetic vapors contained in alveolar cavities shut off by complete bronchial obstruction gradually leave the lung and finally disappear so that the lung becomes atelectatic.

The speed of the disappearance of these gases is proportionate to their solubility coefficient, diffusion speed and to their chemical affinities for substances dissolved in the blood (hemoglobin in the case of oxygen, alkalies in the case of carbon dioxid, etc.).

Since ligature of the branches of the pulmonary artery corresponding to the obstructed lung prevent this disappearance of gases and vapors from the alveoli (Lichtheim, Schlaepfer), it has been concluded that this disappearance is due to absorption by the blood circulating through the lung. However, no direct evidence of this contention has ever been presented.

In this paper a detailed study has been presented of the times of absorption of oxygen, carbon dioxid, nitrogen, hydrogen and helium introduced into a lung previously rendered atelectatic. In this way the absorption times have been determined with considerable accuracy and their absorption has been proven.

Determinations which were carried out by the same technique for anesthetic vapors and gases, namely, ether, ethyl chlorid, nitrous oxid and ethylene showed the great rapidity of their absorption.

Integrity of the alveolar endothelium is just as necessary as integrity of the pulmonary circulation. Edema of the lung produced by injection of concentrated ether vapor into the lung instantaneously stops gas absorption.

Comparative study of absorption by the pleural cavity of oxygen, carbon dioxid, nitrogen, air, hydrogen and helium showed that their absorption is regulated by the same physicochemical laws governing absorption of gases from the obstructed lung.

On the basis of the above experimental findings it has been endeavored to justify our contention that atelectasis always follows complete bronchial obstruction and that it cannot occur without complete bronchial obstruction.

The aim of this investigation has been to offer a direct experimental proof that complete bronchial obstruction is the exclusive cause of atelectasis.

In the third paper of these series a new theory of production of atelectasis will be given.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*

III. A THEORY OF AIR ABSORPTION IN ATELECTASIS.

BY POL. N. CORYLLOS, M.D.,

PROFESSOR OF CLINICAL SURGERY AND RESEARCH ASSOCIATE IN SURGERY,

AND

GEORGE L. BIRNBAUM, M.D.,

RESEARCH ASSISTANT IN SURGERY, CORNELL MEDICAL COLLEGE,
NEW YORK.

(From the Department of Surgical Research, Cornell University Medical College, New York.)

CONSIDERATIONS brought forth in the previous papers of this series lead us to the conclusion that atelectasis is the end result of the interchange between the gases of the alveoli and the perialveolar capillary blood through the pulmonary endothelium. Atelectasis must inevitably follow complete bronchial obstruction as a result of the absorption of the alveolar gases; conversely atelectasis cannot occur unless the alveolar gases are completely shut off from the external air. Incomplete obstruction of a bronchus would mean a renewal by the inspired air of the gases depleted in alveolar absorption.

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In the light of this theory atelectasis depends upon the difference in partial pressures of the gases on either side of this membrane, upon the integrity of the pulmonary endothelium and upon the integrity of the pulmonary circulation allowing the gases absorbed from the alveoli to be carried away from the lung by the blood.

The most important factor in the accomplishment and regulation of this exchange of gases is the difference in partial pressures of the gases in the alveoli and perialveolar capillary blood. Paul Bert showed first that in the alveoli or in the blood it is not the total pressure of the gas mixture, but the partial pressure of each individual gas acting as if it were alone which is of importance. In a

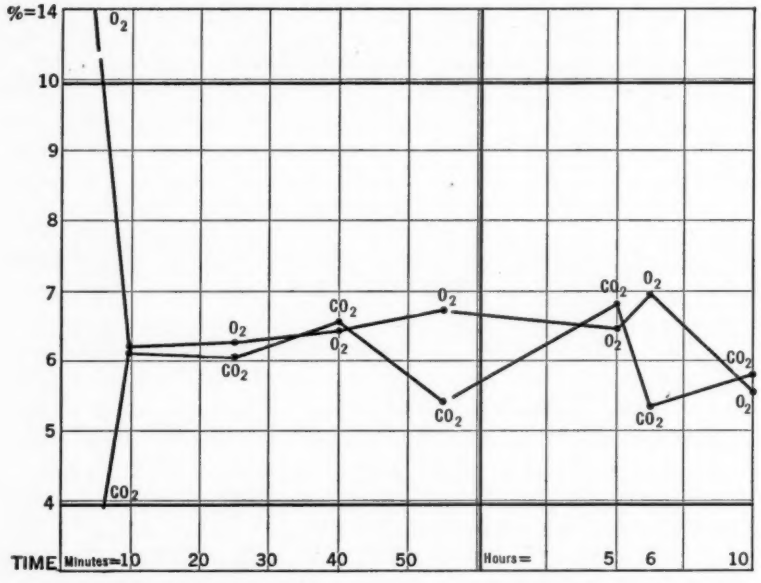

FIG. 1.—Graphic representation of percentages of oxygen and carbon dioxid obtained by alveolar gas analysis before obstruction and for a period of over 10 hours after obstruction of the right lung. Dog 482.

mixture of gases, where no chemical action occurs, each gas behaves independently; this fact is formulated in the law of partial pressures, of Dalton. Thus, if 100 cc. of oxygen and 400 cc. of nitrogen both at one atmosphere of pressure are mixed, the resulting mass of gas occupies 500 cc. at the same pressure. Since equal volumes of gases at the same pressure contain equal numbers of molecules, the mixture contains 4 times as many nitrogen as oxygen molecules in the contained space. This means the nitrogen can exert 4 times as much pressure against a given membrane, for the bombardment and number of its molecules against it is 4 times as great as oxygen. Thus the oxygen acts as if it were under a pressure of only $\frac{1}{5}$ of an

atmosphere ($\frac{1}{5} \times 760 = 152$ mm. Hg), while the nitrogen acts as if it were under a pressure of $\frac{4}{5}$ of an atmosphere ($\frac{4}{5} \times 760 = 608$ mm. Hg).

In Fig. 1 is shown the percentages of oxygen and carbon dioxid obtained by alveolar gas analysis before obstruction of a lobar bronchus and for a period of 10 hours thereafter. Within 10 minutes after obstruction the oxygen has fallen from 15 to 5 per cent and the carbon dioxid has gone from 5 to 6 per cent, showing that an approximate equilibrium with the venous alveolar capillaries has been established. From this point on, a series of gas exchanges takes place, leading ultimately, in 12 to 16 hours, to an atelectasis, as occurred in this case.

TABLE 1.—PERCENTAGES AND PARTIAL PRESSURES OF OXYGEN, CARBON DIOXID AND NITROGEN IN ALVEOLAR AIR AND VENOUS CAPILLARY BLOOD.

Gas.	Alveolar air.		Venous blood.	
	Per cent.	Partial, pressure mm. Hg.	Per cent. of one atmosp.	Partial pressure, mm. Hg.
Oxygen	15	114	5	38.0
Carbon dioxid	5	38	6	45.6
Nitrogen	80	608	..	608.0

Table 1 represents in round figures the percentages of one atmosphere and the corresponding partial pressures of gases in the alveolar and venous air. These differences in partial pressures are possible notwithstanding the continuous exchange of gases through the respiratory membranes, only because the alveolar air is continuously renewed by respiration, by drawing by diffusion on the tidal air filling the bronchi on each respiration. This exchange is so active that in spite of the continuous renewal of air the alveolar air is poorer in oxygen and richer in carbon dioxid than the atmospheric air. It is precisely these differences in partial pressures between alveolar and venous gases which render possible oxygenation of the venous blood and elimination of its carbon dioxid.

It is obvious then that if a bronchus is obstructed the air entrapped in the lung will undergo qualitative changes. Its composition will gradually approach the percentages of the gases of the venous blood which is constantly coursing around the alveoli, carrying away gases which are under excess pressure in the alveoli (oxygen) and giving off gases to the alveoli which it has in excess (carbon dioxid). Such qualitative changes necessarily result in quantitative changes.

In order to simplify the question, we shall graphically represent the alveolus by a circle surrounded by a larger circle which represents the venous blood circulating in the perialveolar capillaries. (Fig. 2.) Further, 100 will represent the volumes of the air content of this alveolus (O_2 15, CO_2 5, N_2 80). After obstruction of

the bronchiolus an equilibrium of gases inside and outside of the alveolus will be established. We shall consider the three gases separately.

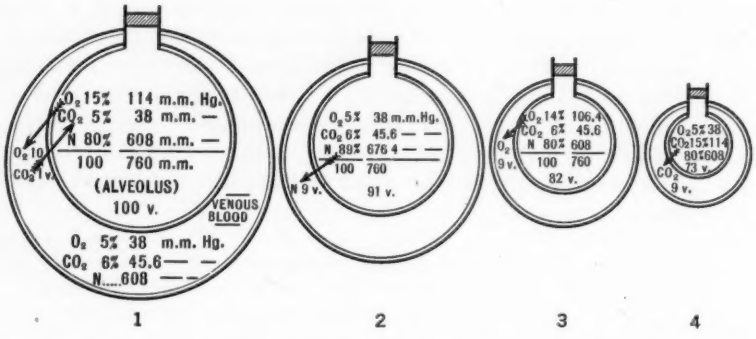

FIG. 2.—A schematic representation of alveolar gas exchanges, gradual gas absorption and shrinkage of the alveoli after complete bronchial obstruction. The absolute volume of the alveolus is only approximately indicated, but the figures are relative and demonstrate perfectly well the principles involved. In 1, 10 volumes of oxygen diffuse into the venous blood and 1 volume of carbon dioxid diffuses out of the venous into the alveolus. In 2, the alveolus has now lost 9 volumes of gas as stated under 1 and oxygen and carbon dioxid have come into equilibrium in the venous capillary blood and in the alveolus. However, the percentage and partial pressure of nitrogen have now been increased so that 9 volumes of nitrogen diffuse out of the alveolus into the venous blood. In 3, 9 volumes of nitrogen having previously diffused out of the alveolus into the venous blood, the percentage and partial pressure of oxygen or carbon dioxid have been relatively increased. For purposes of explanation let us say the oxygen has thus been relatively increased in percentage and partial pressure. Nine volumes of oxygen are now ready to diffuse out of the alveoli into the venous blood. In 4, 9 volumes of oxygen having diffused from the alveolus into the blood, we can consider that the carbon dioxid in the alveolus is relatively increased by these 9 volumes. Thus the partial pressure of this gas is relatively increased and carbon dioxid is ready to diffuse out of the alveolus. Thus the cycle continues until all the gases of the lung are absorbed, although actually the gas exchanges are going on simultaneously and not in the isolated way which we have ideally considered.

Oxygen represents 15 per cent of the gas mixture, and it is under a partial pressure of 114 mm. of mercury in the alveolus, whereas in the venous blood it is present to the extent of 5 per cent of one atmosphere and a partial pressure of only 38 mm. of mercury. (Fig. 2.) Therefore, 10 volumes of oxygen will pass from the alveolus into the blood; at the same time, and for similar reasons, 1 volume of carbon dioxid will pass in the opposite direction from the blood to the alveolus. In this way the gas mixture of the alveolus will lose 9 per cent of its original volume, so that instead of 100 volumes there is now 91 volumes. Now if the alveolar wall were a rigid structure the total pressure of gas in the alveolus would decrease and instead of a pressure of 114 + 38 + 608 = 760 mm. of mercury, it would become 38 + 45.6 + 608 = 671.6 mm. of mercury. Since the alveolar wall is a perfectly elastic structure, it is obvious that the alveolus will retract because the pressure around it is 760 mm.

of mercury. In fact the other lung being in connection with the atmospheric air, the intrapulmonary pressure in it is 760 mm. of mercury (the negative intrapleural pressure of from −4 to −7 mm. of mercury is comparatively so small that it is of little importance in this mechanism).

We shall now consider nitrogen. At the start, before bronchial occlusion, it represented 80/100 of the alveolar gas mixture. Now after the reduction in volume of the gas mixture it represents 80/91 of the gas mixture and its partial pressure has risen from 608 to 676.4 mm. of mercury. But this pressure is much higher than the pressure of nitrogen in the capillary blood; the excess of nitrogen will, therefore, pass into the blood. In other words, 9 volumes of nitrogen will be carried from the alveolus by the circulating blood, so that the volume of the alveolar air will be 91 − 9 = 82 volumes.* (Fig. 2.)

This decrease in alveolar nitrogen disturbs again the equilibrium of oxygen and carbon dioxid between the alveolar air and the venous blood. Let us suppose that oxygen alone is affected by this imbalance. It is obvious that instead of 5 per cent, as it was previously, it will now represent 14 per cent of the alveolar gas mixture (N_2 80 + CO_2 6 + O_2 14 per cent) and, therefore, its partial pressure will rise to 106 mm. of mercury; so that now again 9 volumes of oxygen are ready to be carried away from the alveolus by the circulating blood. When this happens the volume of the alveolus will decrease to 82 − 9 = 73 volumes.

The carbon dioxid will be affected in the same way (Fig. 2), and for similar reasons its percentage will rise from 6 to 15 per cent, corresponding to a partial pressure of 114 mm. of mercury, so that again 9 volumes of carbon dioxid are ready to be carried away by the circulating blood, thus reducing the volume from 71 to 62. The cycle is repeated, and 9 volumes of nitrogen will be ready to pass from the alveolus into the venous blood. Continuing this series of events, there will be a constant oscillation in gas values, and all the alveolar gases will be absorbed. In the open chest experiments we have noted that the initial absorption of gas is slow; after a while the lung seems to shrink much more rapidly; that is, there is an accelerated diminution in the size of the lung. Toward the end of the process when the great mass of gas has already been absorbed the process of absorption seems to slow down markedly, so that one may observe small isolated or patchy areas remaining practically unchanged over a long period of time. This mechanism is explained in Fig. 4, p. 332. The alveolus is represented by a

* These figures are not, strictly speaking, exact; for example, the volume of nitrogen in Fig. 2 = 80/91 = 87.9/100 and the partial pressure corresponding to it equals 667.04 mm. of mercury. We prefer to give the figures as they are, however, because they simplify the explanation without altering any essential relations between the gases.

sphere, the radius of which is 1. The ratio of surface to volume is 3 to 1. Now suppose gases are absorbed so that the alveolus shrinks and its radius is one-half; the ratio of surface to volume is now 6 to 1. In other words, the volume of contained gases has been diminished much more than the surface of the alveolus, and there is relatively twice as much surface for the contained volume of gas as there was previously. This means that there is more absorbing surface for a unit volume of gas, and the alveolus will absorb a greater fraction of its contained volume of gas per unit of time than in the previous case. Thus, with the progressive shrinkage of the lung there is an acceleration in the absorption rate. However, this effect is offset by the impoverishment of the capillary circulation when the alveoli are markedly collapsed, so that in this way we can explain what we have actually observed: a slowing up of absorption toward the end of the process.

It is understood, of course that gas absorption does not occur in the schematic way we have here depicted; actually, there is an incessant simultaneous exchange of all the gases involved. Bohr has shown that extremely small differences in partial pressures are sufficient to insure the diffusion of great amounts of gases through semipermeable membranes. Loewy and Luntz have shown that a difference of only a couple of millimeters of mercury suffices for the passage through the alveolar membrane of the 250 cc. of oxygen per hour per kilogram necessary basically for a man at rest.

We have seen that the anesthetic vapors and oxygen are rapidly absorbed.* It is now easy to understand how atelectasis might develop during the course of an operation as in the cases reported by H. Santee and Bergamini and Shepard. Should complete bronchial obstruction by viscid bronchial secretions occur during the course of an operation and the lung area involved contain a high percentage of anesthetic vapors and oxygen, atelectasis could readily be produced within an extremely short time.

A word should be said further about the rôle played by nitrogen in the gaseous exchanges in the lung. We have seen that it is one of the inert gases, requiring many hours for its absorption. Oxygen and carbon dioxid alone are absorbed by the lung in a few minutes; but when oxygen and carbon dioxid are considered in the atmospheric mixture their absorption periods are greatly prolonged the nitrogen of the air acting as a physical brake by virtue of its slow absorption into the blood. For this reason should bronchial obstruction occur, the time required for the production of atelectasis would be measured in hours rather than minutes. In this way the nitrogen of the air may be considered as a fortunate circumstance of Nature to delay alveolar gas absorption and production of atelectasis. This delay is valuable because it allows an interval

* The reader should refer to the two previous articles of this series.

of time during which reaëration of the lung could still be easily accomplished. Thus nitrogen may be thought of as the "safety brake," especially during anesthesia and the postoperative period, and may be considered as the "mechanical buffer" of the air.

From the foregoing paragraphs it is seen that in the absorption of anesthetic gases and vapors the nitrogen of the air allows their dilution and acts as a "brake," delaying their absorption. Without this gas general anesthesia by inhalation would not be possible.

Comment. There are three possible objections to our theory:

1. An equilibrium between the gases of the blood and alveolar blood could be reached after bronchial occlusion, and this should stop further exchange of gases.

2. Much more carbon dioxid should pass from the blood into the alveoli, because its speed of passage through the alveolar membrane is 30 times as great as for oxygen; thus atelectasis would be impossible.

3. The negative intrapleural pressure on the affected side in atelectasis has often been reported so increased that it was surmised that it should cause a passage of gases from the blood into the alveolus, and in this way prevent atelectasis.

The first objection can easily be answered. If all the gas molecules contained in the obstructed alveolus are absorbed this is due to the perfect elasticity of the alveolar membrane and to the great difference in diffusion speeds through it of oxygen, carbon dioxid and nitrogen. For these reasons a perfect equilibrium is never reached, and as Loewy and von Schroetter first showed, the exchange of gases is represented by an asymptotic curve.

The second objection is based on the great speed of passage of carbon dioxid through the alveolar membrane as compared with oxygen or nitrogen. We have already mentioned the experiment with the frog's lung demonstrating this point. Exner, using a soap film, showed that carbon dioxid would pass through it toward an indifferent gas with a speed of about 10 cc. per minute per square centimeter when under a pressure of only $\frac{1}{2000}$ of an atmosphere. But the rate of diffusion of gases is regulated by their partial pressures, so that, although carbon dioxid passes rapidly from the blood into the alveolus after bronchial obstruction an equilibrium is reached when its percentage becomes about 6 per cent of one atmosphere in the alveolus; after this point the actual mass of carbon dioxid exchanged through the respiratory membrane is small. In other words, the exchanges of carbon dioxid are rapidly accomplished, but the actual amount of carbon dioxid passing through the respiratory membrane is regulated exclusively by the differences in partial pressure of the gases respectively in the alveolar and venous air.

The third objection is of even greater importance. Habliston, in 1928, found the intrapleural pressure on the atelectatic side in

4 cases in man to be −12, −13, −16 and −25 mm. of mercury respectively, as against −4, to −7 mm. on the unaffected side. Farris reported 2 similar cases in which relief was obtained by artificial pneumothorax. Wilson and Gordon (quoted by Hablis-ton) and Ashbury have also reported such cases. Ashbury reported a case with a negative intrapleural pressure of −16 to −20 mm. of mercury; after inducing a partial pneumothorax on the affected side with 600 cc. of air the pressure became −4 to −7 mm. of mercury.

Presumably, with a negative intrapleural pressure of −16 to −20 mm. of mercury the intrapulmonary pressure is also −16 to −20 mm. of mercury below atmospheric pressure, for the gases in the lung are under a pressure which tends to be equal to the intrapleural pressure. In the case of a lung which is completely obstructed the pressure of gases within it tends to equal the intrapleural pressure because of the elasticity of the alveoli; thus, if the intrapleural pressure were −20 mm. of mercury the intrapulmonary pressure would also be about 20 mm. of mercury less than atmospheric, *i. e.*, about 740 mm. of mercury. If we consider the percentages of oxygen and carbon dioxid in the entrapped alveolar air as 5 and 6 per cent, of one atmosphere respectively, their partial pressures would be 38 and 45.6 mm. of mercury when the intrapulmonary pressure is 760 mm. of mercury and 37 and 44.4 mm. of mercury with an intrapulmonary pressure of 740 mm. Therefore, in the case under consideration the effect of a −20 mm. negative intrapleural pressure would be to lower the partial pressure of oxygen and carbon dioxid in the alveolus by only from 1 to 2 mm. However, it must also be remembered that the gases in the alveolar capillary blood are also subjected to corresponding diminution in their pressures, so that from a relative standpoint the partial pressures of the gases in the alveoli and in the alveolar capillaries have not changed. We may thus deduce that the increased negative intrapleural pressure does not materially influence the exchange of gases in the obstructed lung.

So far as the therapeutic effect of artificial pneumothorax is concerned, we agree with the foregoing authors quoted, as to its palliative effect by decreasing the displacement of the heart, but we completely disagree as to its efficacy in freeing the air passages of obstructing material. Pneumothorax cannot further compress a lung already atelectatic. Lastly, collapse of the lung by pneumothorax does not favor reaëration or penetration of air into this lung; on the contrary, deeper respiration by producing dilatation of the bronchi is more apt to lead to the formation of airways between obstructing mucus and bronchial wall with subsequent expulsion of the obstacle to respiration.

Increased pressure of the entrapped air as produced in coughing or strained respiration would theoretically accelerate the absorp-

tion of the alveolar gases, as has been maintained by van Allen and Adams. We think, however, that these authors have greatly exaggerated the importance of the factor, for an increase in intrapulmonary pressure in the obstructed lung can in these cases be produced only by an increase in the intrapulmonary pressure of the healthy lung. This means an increase in total intrathoracic pressure and consequently in the blood and blood gases as well. It seems that in these cases of van Allen and Adams, if atelectasis was produced earlier in animals incompletely anesthetized and struggling, this was due rather to excessive muscular work and exhaustion of oxygen in the blood, while at the same time rapid breathing washed out the carbon dioxid of the blood; the percentages of both gases and their partial pressures in the blood were decreased, causing a more rapid absorption of the entrapped air. We do not think, however, that from their data these authors were justified in coming to the conclusion that "narcotics are advisable because they aid in preventing atelectasis." The chief means the lung possesses to prevent atelectasis, or to overcome it once the bronchus is obstructed, is expulsion of the bronchial exudate by cough and deep breathing. Narcotics, on the contrary, deprive the lung of its best means of defense. We believe that for reasons previously described the more efficient treatment (both preventive and curative), besides rolling of the patient from side to side and encouraging him to breathe deeply, is hyperventilation by repeated inhalation of 10 per cent carbon dioxid in oxygen, (according to the method introduced by Henderson and Haggard in resuscitation after carbon monoxid poisoning), or bronchoscopic aspiration of bronchial exudate.

For a number of years we have endeavored to show that atelectasis is a well-defined clinical syndrome with a definite etiology, pathogenesis, pathology and treatment. It presents various clinical forms which can briefly be distinguished as follows:

1. According to the etiology: obstructive or compressive, postoperative or medical.
2. According to its distribution: multilobar (massive), lobar or lobular (patchy).
3. According to its duration: acute or chronic.
4. According to its evolution: simple or complicated.

The last variety comprises the cases in which infection follows because of the presence of the obstructing agent of microbes of more or less high virulence, so that an infectious process begins in the lung and is favored by the impaired drainage of the respiratory organ. Postoperative atelectasis in which Group 4 pneumococcus is always present represents a mild form of infection. Lobar pneumonia in which more virulent pneumococci are present represents another type of acute infectious atelectasis occurring as an accident in the course of pneumococcic bronchitis. Abscess and gangrene

of the lung are similarly infectious forms of septic bronchial obstruction and atelectasis, due to specific microörganisms, aërobes and anaërobes. The painstaking work of Smith, Allen, Joannides and others throws a new light on this last variety, justifying our conception.

We have also endeavored to prove that the pathologic process in the different forms of atelectasis develops along the same lines as in similar lesions in glandular organs, the ducts of which have been obstructed and to which the lung should be compared. We have shown that the circulation and the ventilation in lungs that have become atelectatic, from any cause, show exactly parallel changes, depending entirely on the condition of the pulmonary ventilation.

The present work, by showing the intimate mechanism of the production of apneumatosis, can explain the pathogenesis of the different forms of the disease by sound physiologic principles. It shows, further, the importance of physiologic, physical and chemical consideration in the study of respiration in relation to thoracic surgery. Clinical and experimental evidence points to the conclusion that atelectasis is always due to complete bronchial obstruction. We wish to stress the great importance in the pathology of the lung of impairment of free bronchial drainage, and we believe that it has been demonstrated beyond doubt that atelectasis must be definitely associated with the idea of bronchial obstruction. The obstructing agent, whatever its nature, should be sought and treatment instituted for its removal and reaëration of the lung.

General Conclusions. 1. Experimental methods have been devised which give evidence that when a bronchus is completely obstructed the entrapped alveolar air rapidly undergoes qualitative and quantitative changes as determined by successive gas analyses.

2. Qualitatively, the percentages and partial pressures of the gases comprising the alveolar air tend to, but never quite, reach an equilibrium with the gases of the venous blood.

3. Quantitatively, the entrapped alveolar gases pass through the respiratory membrane into the blood circulating in the perialveolar capillaries until complete airlessness of the involved area is produced.

4. The mechanism of production of atelectasis in the compressed lung (pneumothorax, pleural exudate, intrathoracic tumors, etc.) is exactly the same as in bronchial obstruction.

5. Besides the gases of the air, diffusion of other gases was studied by introducing them into a lung previously rendered atelectatic. The different gases used in these experiments were: (*a*) Active gases, oxygen and carbon dioxid; (*b*) neutral gases, hydrogen, nitrogen and helium; (*c*) anesthetic gases or vapors, ether, ethyl chlorid, nitrous oxid and ethylene.

6. A new experimental method was devised which allows direct vision of the pulmonary changes occurring during the experiment.

7. Nitrogen in the respiratory air plays the part of a "mechanical buffer," retarding the absorption of more diffusible and more soluble gases.

8. This experimental work has allowed the formation of a theory on the mechanism of atelectasis based on the physiology of exchange of gases in the lung.

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THE PATHOLOGY OF RHEUMATIC PNEUMONIA.

By Benjamin A. Gouley, M.D.,

ASSISTANT INSTRUCTOR IN PATHOLOGY,

AND

John Eiman, M.D.,

PATHOLOGIST TO THE PRESBYTERIAN HOSPITAL, PHILADELPHIA, PA.

(From the Laboratories of the Philadelphia General Hospital, Presbyterian Hospital and the Department of Pathology of the University of Pennsylvania Medical School.)

The pulmonary manifestations of rheumatic fever have been studied by many clinicians. Many years ago Fuller,[1] Cheadle,[2] Garrod[3] and other English physicians wrote of "Rheumatic Pneumonias." It is probable that these earlier writers recognized clinically lesions similar to those which are the subject of this report. Some of their observations correspond very closely to what is today being identified as the clinical picture of rheumatic pneumonitis and rheumatic pleurisy. Garrod mentioned the transient character of the physical signs of the pulmonary lesions, but he stated that there is nothing peculiar in the postmortem appearance of such a lung or its pleura which would differentiate it from the ordinary acute inflammations.

Pulmonary lesions in the course of rheumatic fever are certainly not infrequent, as evidenced by the reports of Fuller,[1] Latham,[4] Cheadle,[2] Garrod[3] and in recent years by Thayer,[5] Swift,[6] Rabinowitz[7] and Paul.[8] They have been recognized rather commonly in the more severe cases of rheumatic fever studied by Dr. J. C. Small and ourselves at the Philadelphia General and Presbyterian Hospitals.

Until very recently, knowledge of the incidence and character of these changes has been based mostly on clinical observations. Pathologic study was inconclusive.

Among the lesions which others have described are: (1) Rheumatic fibrinous pleurisy; (2) rheumatic pleurisy with effusion; (3) atelectasis secondary to pleural effusion; (4) atelectasis secondary to

enlarged heart or pericardial effusion; (5) vascular lesions, involving the pulmonary aorta and its branches.

The above list does not include the pulmonary changes commonly caused by cardiac decompensation, such as hydrothorax, passive congestion and infarction of the lung, both static and embolic.

Rheumatic pleurisy, meaning a specific inflammatory lesion, similar to rheumatic pericarditis and polyarthritis, was among the earliest recognized features of rheumatic fever. Despite the fact that it was accepted as a rheumatic manifestation, little attempt was made to establish its status by pathologic description. Longstreth,[9] of the Pennsylvania Hospital, described the marked fibrinous character of this pleurisy and pointed out the rarity of empyema as a complication. Bezançon and Weill[10] studied the chemical composition of the pleural effusion with especial reference to its fibrin content. They, as well as others, recorded a predominance of endothelial cells in rheumatic pleurisy. In 1928, Paul[8] made an excellent review of the history of the pleural and pulmonary lesions and described the specific nature of the pleurisy.

The vascular lesions are the specific changes that have been observed in the pulmonary artery, its branches, and especially the arterioles. They are identical with the vascular lesions seen in the aorta and in many of the viscera and are characteristic of rheumatic fever. Other acute infections are known to produce focal necrotic lesions in the aorta and the arterial branches, but rheumatic fever is now recognized as the most important cause of this type of lesion. Discovery of this vascular damage has been a recent contribution to the rapidly-increasing knowledge of the nature of rheumatic fever.[11] Acute rheumatic involvement of the pulmonary aorta and its larger branches has been of little or no clinical significance.

Pleurisy is a common manifestation of the serous membrane involvement in the active stages of the disease. Undoubtedly it has been the cause of many, or in certain cases most, of the physical signs that led to the diagnosis of "rheumatic pneumonia," and to the unusually high incidence of that complication in the statistics of Latham and Fuller. It is seen in the majority of those cases that have come to necropsy in the acute or subacute phases of rheumatic fever. It may be present in most extensive degree, accompanying a widespread mediastinitis and pericarditis, productive of the classical signs and symptoms of acute pleurisy, and is then usually followed by effusion. It also may exist in small isolated patches of fibrinous exudate, usually over the lower lobes and to a lesser degree on the upper lobes. These smaller patches, as with similar lesions on the epicardial surface are seldom detected by physical examination. We are entirely in accord with Paul's findings as to the frequent incidence of rheumatic pleurisy, and as it is not the subject of this report the reader is referred to his article for its detailed description.

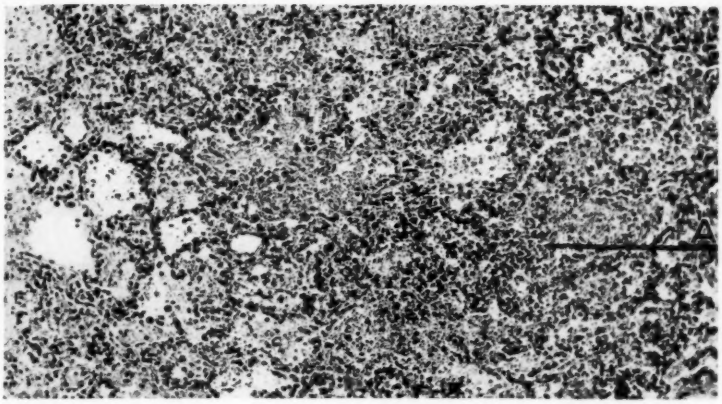


FIG. 1

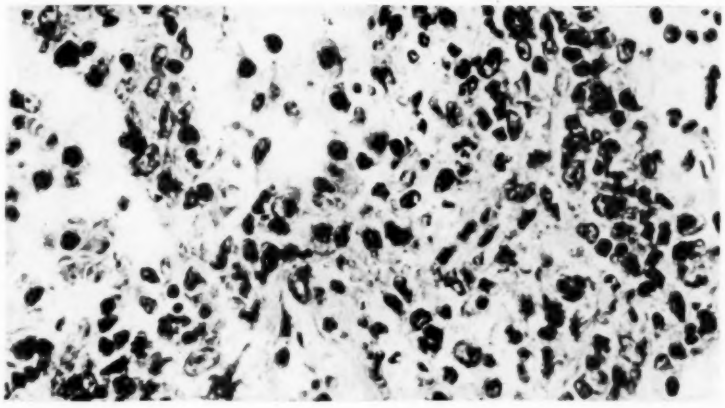


FIG. 2

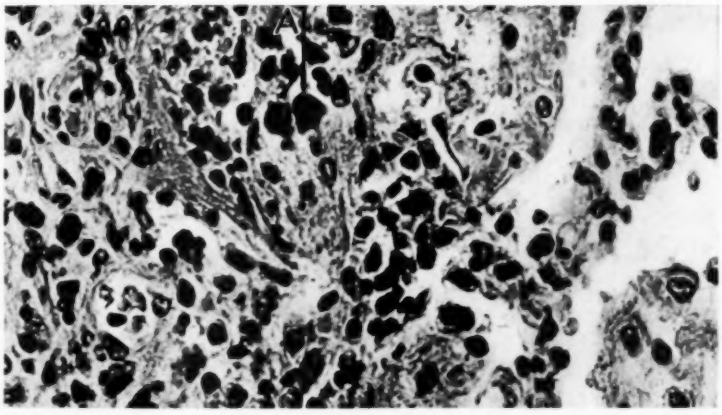


FIG. 3

FIG. 1.—(Case 1.) Low power; rheumatic pneumonia. The alveoli are filled with blood and fibrin; the walls are thickened with inflammatory exudate (*A*).

FIG. 2.—(Case 1.) High power, showing interstitial infiltration, consisting mostly of endothelial cells and fibrin. Many cells are pyknotic. The cellular content of the alveoli is scanty. (× 552.)

FIG. 3.—(Case 1.) Dense infiltration, with obliteration of the alveoli. Note large basophilic cells, and Aschoff cells with two or three nuclei (*A*).

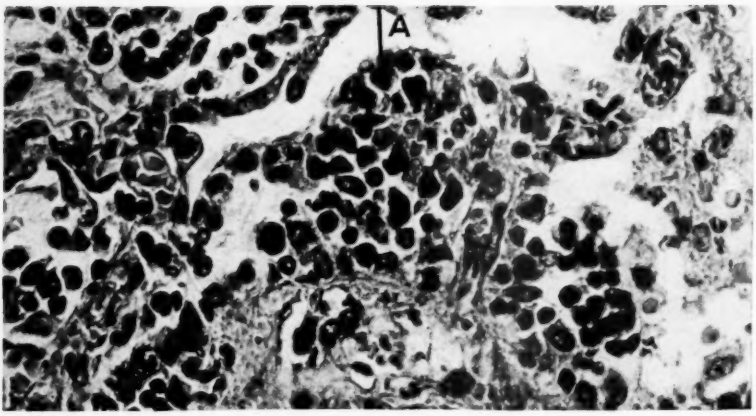


FIG. 4

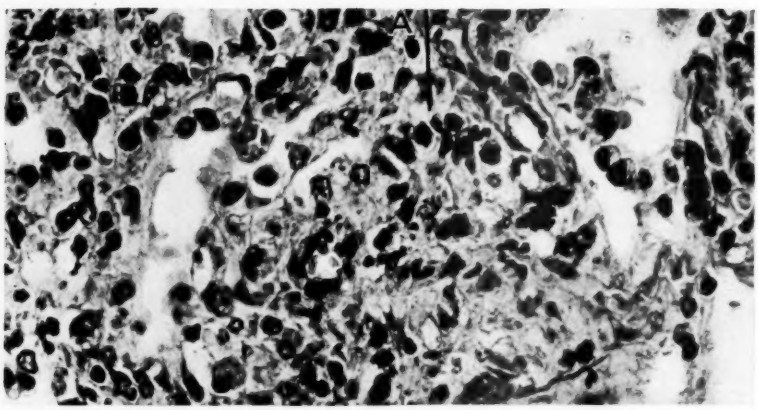


FIG. 5

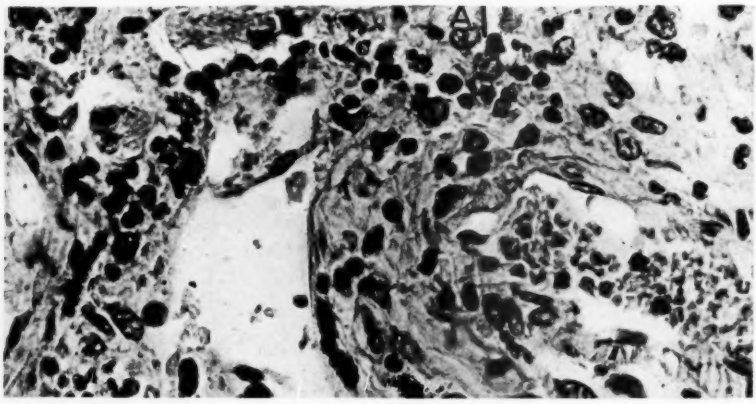


FIG. 6

FIG. 4.—(Case 1.) Perivascular nodule of large basophilic cells (proliferative lesion). Note bulging of the lesion into the alveolus. (× 552.)

FIG. 5.—(Case 1.) Showing early necrotic interstitial focus. Note irregular concentric arrangement of epithelioid cells (*A*).

FIG. 6.—(Case 1.) An arteriole showing invasion of the adventitia and media by a submiliary nodule (*A*). It does not reach the intima. (× 552.)

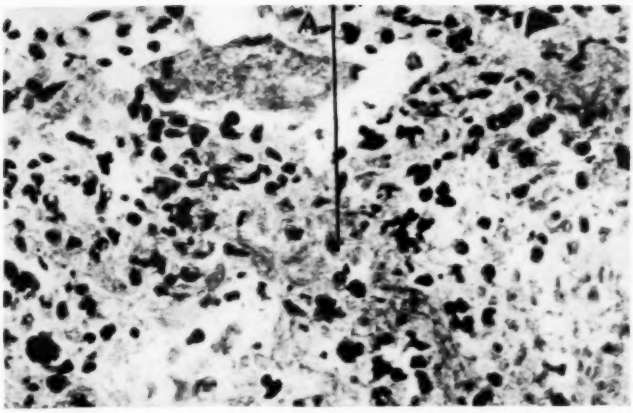


FIG. 7

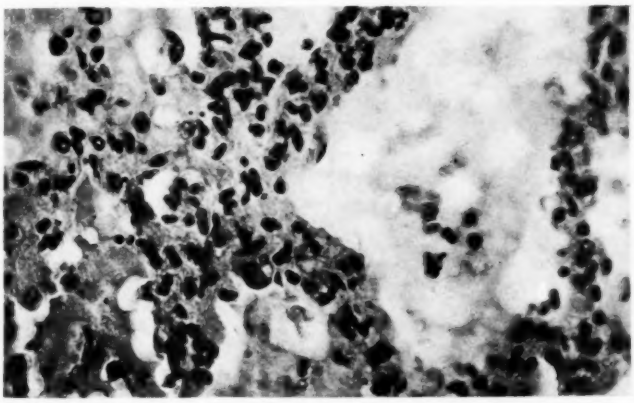


FIG. 8

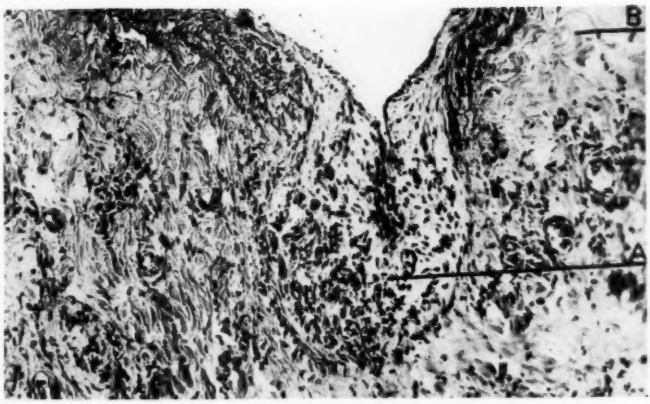


FIG. 9

FIG. 7.—(Case 3.) Rheumatic interstitial pneumonia. The alveolar walls are necrotic and are converted into broad irregular bands of fibrin (*A*). The infiltrating cells are the irregular epithelioid types. One giant cell is seen in the lower left corner. The alveoli contain erythrocytes.

FIG. 8.—(Case 5.) Acute infiltration of irregular epithelioid cells and fibrin in the alveolar walls. Fibrin and serum fill the alveoli.

FIG. 9.—(Case 5.) Rheumatic nodule in wall of pulmonary artery (*A*). Hyalinized and vascularized adventitia (*B*).

FIG. 10

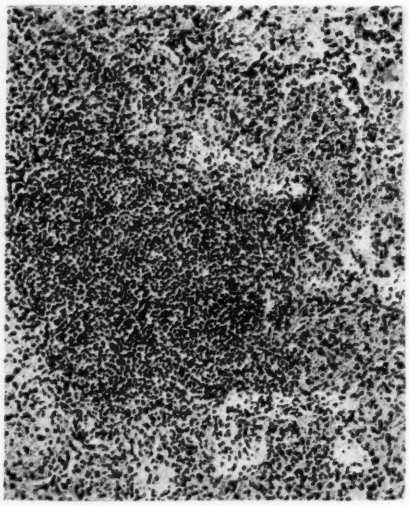
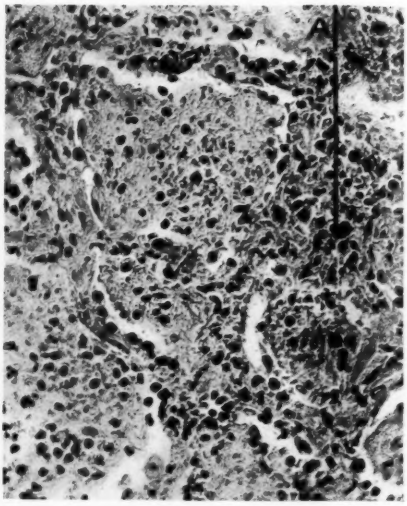


FIG. 11



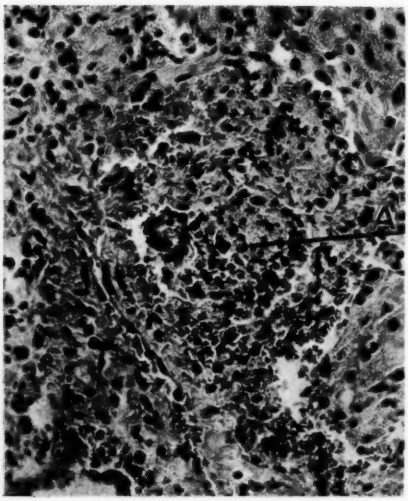


FIG. 12

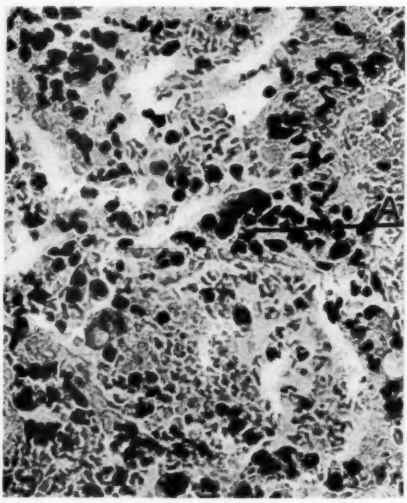


FIG. 13

FIG. 10.—(Case 6.) Unusually large nodule in rheumatic pneumonia, consisting of endothelial, epithelioid and polymorphonuclear cells. The adjacent lung tissue is completely consolidated.

FIG. 11.—(Case 6.) Rheumatic pneumonia showing Aschoff nodule (*A*), with many of the alveolar walls converted into strips of fibrin. The alveoli are filled with fibrin and blood and some contain a few polymorphonuclears and endothelial cells.

FIG. 12.—(Case 6.) Aschoff nodule in rheumatic pneumonia.

FIG. 13.—(Case 6.) Typical Aschoff nodule in the alveolar wall (*A*). The adjacent interstitial tissue is invaded by epithelioid cells. The alveoli are filled with red blood cells and fibrin.

Patients with rheumatic fever, particularly if severe, may frequently exhibit a clinical picture suggestive of lobar pneumonia. This pulmonary involvement may appear about the same time as do the acute cardiac disturbances; it is usually preceded by the appearance of arthritis, but certainly not in every case. The symptoms common to acute rheumatic fever are, of course, seen with this pneumonitis. It does not depend apparently upon the presence of an upper respiratory infection, differing thus from the usual bronchopneumonia; it does not present the striking features of the classical picture of lobar pneumonia—chill, prolonged and high fever, rusty sputum, severe pleural pain and marked elevation of the respiratory rate. On the contrary, its symptoms are usually not spectacular; initial chill, heralding the pulmonary invasion, does not occur; cough may, or may not, be troublesome; it is productive of a scanty tenacious sputum, presenting no special bacteriologic findings; occasionally it may be blood streaked. The fever is irregular; it is often high (102° to 105° F.), reflecting the severity of the general infection. There is a moderate elevation of the respiratory rate.

The physical signs assume a greater prominence than do the symptoms. Dullness to percussion and bronchial breathing are frequent and characteristic findings. They may be found at the bases in either lung, laterally in the axillary areas, or even in the upper lobes. One entire lobe may appear to be involved; two or more areas may be consolidated at the same time. A striking feature in many cases is the transient character of the several consolidations, analogous to the course of the polyarthritis. In some cases the signs of consolidation may be prolonged as much as a week or more. It usually lasts from 2 to 4 days. Consolidation may recur in the same area within a few weeks in unusually virulent infections. The signs of consolidation are often followed by dullness with absence of breath sounds due either to pulmonary collapse or pleural effusion. Such signs may persist for many days or weeks. Râles may or may not be present in the stage of consolidation. They are of variable quality and seldom, if ever, are heard in the same number and intensity as in lobar pneumonia. In the later stages, large and coarse friction râles are frequently heard and can be ascribed to a plastic pleuritis.

The signs of consolidation, according to the best authorities, represent atelectasis rather than an actual pneumonitis. The statistics of Latham, made over 80 years ago, are in disrepute, being based mostly on unsupported clinical observation. That the striking pulmonary signs heard in these acutely ill patients are not caused solely by pleurisy has been the conviction of a number of observers. Bezançon and Weill[10] and Goyena[13] employed the term "corticopleuritis" to indicate that a subpleural zone of congestion or inflammation existed together with the pleurisy. The lesion was

described as "splenization" by Besnier,[14] *i. e.*, not a real exudative lesion, but rather an intense hyperemia and edema with collapse and atelectasis of lung tissue. Coombs,[15] the English authority on the pathology of rheumatic fever, considered atelectasis and passive congestion as the chief lesions in the production of these signs. However, he mentions the possibility of consolidation appearing in in the right upper lobe, an area relatively immune from the complicating influence of cardiac failure.

If a pneumonia does exist, is it a specific lesion? Garrod did not think so.[3] Occasionally lobar pneumonia, due to the pneumococcus, complicates acute rheumatic fever, and other infections have been encountered. Thayer,[5] reporting a series of 25 fatal cases of rheumatic fever, noted terminal pneumonia or bronchopneumonia in 50 per cent of the cases. Paul[8] noted that in more than half of 30 cases, there were evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or groups of lobules, which might be interpreted as an early or hemorrhagic state of broncho- or lobular pneumonia. Certain atypical features were present, *i. e.*, the extremely hemorrhagic character of the intra-alveolar exudate and a difficulty in isolating the commoner types of bacteria usually associated with bronchopneumonia. Although it seems to have been a fairly characteristic finding in his cases, he did not think that the evidence warranted its description as a specific lesion. He came to the conclusion that such a lesion limited to individual lobules was insufficient to give rise to appreciable areas of dullness to percussion and that the widespread physical signs were caused by other processes, notably pulmonary atelectasis and pleural effusion.

Rabinowitz,[7] in a recent discussion, concluded that a specific pneumopathy did occur, clinically distinguishable from lobar pneumonia and from bronchopneumonia and that the ultimate proof of its existence would be made with the discovery of Aschoff lesions in the consolidated lung.

The chief stumbling block in according this rheumatic pneumopathy a specific status has been the absence of a precise pathologic description, which in turn depends on the fact that few cases of rheumatic fever die in the course of an acute attack, especially in the initial attack, where pulmonary changes are not clouded by the evidence of chronic cardiac failure that has been produced by successive attacks of the disease.

A study starting in 1927 of the pulmonary lesions in a small series of fatal cases of acute rheumatic fever has convinced us that the clinical picture of consolidation depended upon the presence of a specific pneumonia or pneumonitis. It was specific in that the lesions were essentially those characteristic of rheumatic fever elsewhere in the body and had developed in patients who had rheumatic fever with acute cardiac involvement. A preliminary report of

this lesion, hitherto undescribed as far as we know, was made at a meeting of the Philadelphia Pathological Society in December, 1927.[16] Naish,[17] a short time afterward, described pulmonary lesions in rheumatic fever that are strikingly similar to those we then presented.

This report is based upon the study of 9 fatal cases of acute rheumatic fever that presented pulmonary lesions. Six of the patients were from the Philadelphia General Hospital, 1 from the Presbyterian Hospital, another from the University Hospital, through the kindness of Dr. Baldwin Lucké, and the ninth case from the Jewish Hospital.

Case Reports. CASE 1.—A. N., a boy, aged 11 years, was admitted to the Philadelphia General Hospital on June 11, 1927, and died June 21, 1927. For 2 weeks he had painful swelling of various joints. On admission the arthritis had largely subsided, but he was apathetic and toxic. The temperature ranged between 100° and 103° F.; the pulse rate was 120 to 140 and the respiratory rate was 26 to 30; the leukocyte count was 19,000. Cardiac examination revealed a double murmur at the apex. There had been a previous attack of rheumatic fever 2 years before. On June 14 there was noted a pericardial friction rub and a suggestion of choreiform twitching. On June 15 there was dullness and bronchial breathing over the left base, posteriorly. June 16 there was noted, in addition, dullness over the right base. On June 18 the choreiform movements became marked. The pulmonary signs were practically the same. The patient became very toxic, constantly twitching and suggesting cerebral involvement. He died on June 21.

Gross Morbid Anatomy. There was an acute pancarditis: mitral and aortic valvulitis, rheumatic myocarditis and fibrinous pericarditis. The outer surface of the pericardium, especially on its right aspect, was covered with a very thin fibrinopurulent exudate which also covered the adjacent mediastinal pleuræ. Cultures from the pleural and pericardial exudates, the heart blood and lung tissue were sterile over several weeks. About 300 cc. of fairly clear serous fluid were removed from the right pleural sac and about 100 cc. from the left.

Lungs. The mucosa of the trachea and large bronchi was moderately congested.. The peribronchial and mediastinal lymph nodes were enlarged, soft and edematous. Both lungs showed the same unusual changes. They were moderately enlarged, bulky and did not collapse. They presented a rich variation in color: the lower lobes were solid and deep blue, which contrasted with the yellow or the grayish-white of the more aërated tissue. Smaller reddish-pink and brownish patches were scattered over the entire pleural surface. On section the tissue was dark reddish-brown in color. The surface of most of the cut section of the lower lobe was firm, non-crepitant and unusually smooth as compared to the granular surface presented in lobar pneumonia. The surface was fairly dry in its most airless portions, but somewhat edematous toward the outer part of the lobe. Blocks of tissue from these heavier portions of the lower lobes sank in water. This infiltration differed from an ordinary lobar or lobular pneumonia by the fineness or absence of the granularity, by a smooth liver-like consistency almost resembling atelectasis, but without any gross evidence of collapse, the lungs remaining bulky. On detailed inspection a very fine grayish lattice work, outlining lobules, was noted.

Pathologic Histology. A number of sections taken for histologic study show an acute inflammation of the lung tissue, which manifests itself as

an interstitial cellular infiltration and an alveolar exudate. The interstitial involvement is the more significant of the two (Figs. 1 and 2).

The alveolar walls are thickened because of capillary congestion, edema and cellular exudate. These lesions are not uniform in their distribution. The interstitial tissue sometimes appears slightly prominent because of capillary congestion; in other places it is markedly thickened by cellular infiltration, coalescing in many places into dense aggregations. In such areas the alveolar walls have disappeared and the normal lung architecture is obliterated (Fig. 3). Fibrin, in a liberal amount, appears within the infiltrates. These cellular collections, which are often of nodular or seminodular appearance, seem to start in perivascular locations, gradually radiating out into the interstitial spaces. Practically all are in intimate relationship with bloodvessels, large or small (Fig. 4). The edematous and fibrinous quality of this perivascular infiltration is striking.

The cellular complexion of these lesions is not constant. Most prominent are large, deeply stained cells, with vesicular nuclei, often multinuclear and markedly basophilic (Figs. 3 and 4), sometimes comprising the larger part of the exudate. One also notes a varying number of plasma cells, lymphocytes and an occasional polymorphonuclear. Fibrin and detritus help complete the picture. The large cell with vesicular nucleus, described here stained with methyl pyronin stain (Pappenheim stain), shows a reddish cytoplasm. These cells are known in the submiliary nodules of rheumatic fever as the Aschoff cell; their origin from the lining endothelium of small bloodvessels is accepted by many and they will be referred to in this report as endothelioid cells.

In other fields one notes a fairly large cell, not quite the size of the large Aschoff cell and with an irregularly shaped nucleus that is very deeply stained. The cytoplasm shows a basophilic reaction. The shape of the nucleus may be roughly oval or comma shaped, or sometimes triangular or arrow shaped. These cells are seen side by side with the larger cells and in some areas almost to the exclusion of the latter.

There is also seen a more slender and elongated and much more irregular cell, almost all nucleus, identical in appearance with the epithelioid cell of a tubercle. They very probably have an endothelial origin in common with the other cells described, but their difference in appearance and manner of deposition should be emphasized. In this report they shall be referred to as epithelioid cells. They are seen best in the small focal lesions, apparently very early foci, in which the giant cells are not present. There is a central necrosis composed of fibrin, swollen and broken up connective-tissue fibers, into which these epithelioid cells infiltrate. Together with the larger solidly nucleated cells they frequently present a concentric arrangement around the center of the lesion, or their grouping may present ring-shaped or rosette-shaped figures (Fig. 5). There is a superficial resemblance of these lesions to a tubercle, but there is one essential difference—the tubercle is avascular.

The alveoli are filled with serum and blood where the inflammatory process is most acute. The alveolar contents vary directly in amount with the degree and acuity of the interstitial involvement. In general the cellular constituent of this alveolar exudate is scanty. The lining epithelium is desquamated and often no other cells are seen within the air sacs.

Cellular prolongations of the interstitial infiltration are seen pushing their way into the alveoli, and so these large cells and accompanying lymphocytes can be seen free in some broken-down alveolar spaces.

Very occasionally one notes a few sacs packed with polymorphonuclears. However, this whole pathologic picture is characterized by their absence or, at best, their scantiness. They are present in modest numbers in the small foci of necrosis.

The bronchial branches show no evidence of mucosal inflammation but most of the bronchioles do show a peribronchial cellular infiltration of the type described above, with increased vascularity and edema. This infiltration may surround the whole tube or invade it locally in seminodular appearance.

Sections of the pleura show no exudate or very little. Sections from the mediastinal pleura have not been included. In most places the endothelial surface is intact. The subpleural tissue, however, is thickened from cellular infiltration, invading and obliterating the subpleural alveoli.

The bloodvessels throughout the lung are congested. Perivascular edema, even around the capillaries, is marked. Although many of the vessels are packed with erythrocytes, no definite thrombi are noted. The smaller vessels, arterioles and venules show a marked endothelial hyperplasia. The capillaries and lymphatics occasionally show this as well. The perivascular infiltration at times appears contiguous with the cells of the capillary endothelium, giving the impression that these large cells are of endothelial origin. In the walls of the larger vessels there are occasional infiltrations extending into the adventitia and media (Fig. 6). They do not appear in these sections to invade the intima nor to reach the endothelial surface in the large bloodvessels. Weigert stains do not show any definite destruction of the elastic fiber in these larger vessels, but damage is found in many smaller vessels.

Summary. The histologic study of these lungs showed an acute interstitial inflammatory process, characterized by hyperemia, edema, and a perivascular infiltration of large endothelioid cells, multinuclear giant cells, plasmocytes, lymphocytes and relatively few polymorphonuclear leukocytes. The staining and general appearance of the endothelioid and giant cells are identical with those found in the Aschoff lesions occurring in the myocardium of the same patient.

Case 2.—F. R., male, aged 19 years, was admitted to the Philadelphia General Hospital on June 6, 1927, to the service of Dr. J. C. Small; he died June 28, 1927. At the age of 13 years he had an attack of rheumatic fever which confined him to bed for 8 months. The chief complaints on entering the hospital were joint pains, dyspnea and profuse sweats. The heart was enlarged and its action irregular. There were double aortic and mitral murmurs and a Corrigan pulse. On June 14 distant breathing sounds and moist râles were heard over the right lung, anteriorly and laterally in the third interspace. On June 15 a pleural friction rub at the right base was noted. The râles had disappeared within 2 days but the breath sounds remained distant and were accompanied by coarse friction sounds. The cardiac disease and pleurisy were the outstanding clinical manifestations. Death occurred from heart failure.

Gross Morbid Anatomy. Both pleural sacs were partially obliterated by numerous, rather easily broken fibrous adhesions, which provided sacculations, especially at the bases, and were filled with slightly turbid fluid, about 50 cc. from each side being recovered and cultured with negative results. In some sacculations the fluid was almost gelatinous.

The lungs, heart, trachea and esophagus were removed *en masse*. The peribronchial and mediastinal lymph nodes were soft and edematous but not much enlarged. The pericardial sac was completely obliterated by fibrous adhesions. There was marked acute exopericarditis manifested by violaceous hyperemic patches, without purulent change, extending to and

involving the right mediastinal pleura. The heart was greatly enlarged and showed aortic and mitral valvulitis and sclerotic infiltration of the ventricular membranous septum.

The left lung weighed 380 gm. It was of the normal grayish-pink color and air-containing throughout, except at the base where collapse had occurred. The pleural surface was covered with edematous fibrous adhesions. The lower lobe, posteriorly, showed an acute fibrinous pleurisy. There were many hyperemic areas with the pleural surface gray and translucent, through which very small subpleural nodules could be seen. There were no areas of definite consolidation. On section the lung tissue was grayish-red and crepitant, except for the atelectatic zone at the base. No pus could be squeezed out of the bronchioles.

The right lung weighed 350 gm. It was similar to its fellow, showing the same type of pleural pathology, areas of localized hyperemia, an absence of bronchial inflammation and consolidation, but showing also some basal atelectasis.

Pathologic Histology. The pleura is thickened by a cellular infiltration that is accompanied in some areas by edema and in other areas by a hyaline fibrosis. The infiltration consists mainly of large mononuclear cells, with vesicular basophilic nuclei and cytoplasm. They are diffusely and densely distributed, the only suggestion of localization being around small bloodvessels, whose walls are lined by the same type of cell seen throughout the tissue. Lymphocytes occur in smaller numbers. Polymorphonuclears are present, but only in the fibrinous exudate on the pleural surface. Giant cells appear occasionally.

This endothelioid infiltration extends down into the underlying lung tissue, gradually fading out, giving a distinct thickening of the interstitial walls, blending into the atrophy of emphysema. A few irregular epithelioid cells are also present. Some of the subpleural fibrous tissue is very much swollen, resembling acutely hyalinized fibers. They are swollen, broken up and infiltrated by these large endothelioid cells. The alveoli contain no exudate and only slight desquamation of epithelial cells appears.

The large bloodvessels do not present any abnormalities. They are congested, but do not show any thrombus formation. The smaller vessels exhibit thickened walls and, especially in the areas where the cellular changes are most marked, an extraordinary degree of hyperplasia of the endothelium. Occasionally "Herzfehler" cells are seen in the tissues and a few in the alveoli.

Summary. Acute and subacute pleurisy; subacute and chronic interstitial subpleural pneumonitis; basal atelectasis.

CASE 3.—E. H., a white girl, aged 15 years, entered the Philadelphia General Hospital on the service of Dr. McLean on June 2, 1928. She had been treated in a tuberculous clinic for 3 months because of fever and blood-streaked sputum. On admission the patient was found to be extremely weak, thus preventing a thorough physical examination. She had marked anemia, a leukocytosis, an enlarged heart with signs of mitral valvular disease, a mild icterus and an enlarged, tender liver. There was a history of chorea and growing pains 3 years ago. In the lung examination the resident physician found posteriorly, in both lower lobes, dullness on percussion, distant breath sounds and a few fine crackling râles. Death occurred on June 5, 1928. Diagnosis: myocardial degeneration and anemia.

Gross Morbid Anatomy. Heart: hypertrophy and dilatation and rheumatic pancarditis. There was an acute verrucal endocarditis of the aortic valve, a mitral stenosis, characteristic left auricular pathology and a fatty degeneration of the myocardium. Pericarditis was not present.

The left lung weighed 530 gm., the right lung 520 gm. Both lungs showed the same unusual changes. They did not collapse but remained bulky. The lower lobes contained large consolidations, occupying their larger part and extending up toward the hilum. These areas were of a dark-blue color and quite sharply outlined against the surrounding aërated tissue. The lower part of the upper lobes contained similar firm and dark blue infiltrations along the interlobar fissure, but the apical portions were pale and emphysematous in marked contrast and were spotted and splotched by small, bluish-red foci of hemorrhage. The pleura showed no changes except a slight dullness over the consolidations. In these locations there was noted a thickening of the lymphatics and interlobular partitions, which formed a prominent grayish-white network. The lower lobes, on section, showed well-demarcated areas which were solid, brownish-red in color, with a finely granular surface and without any points of suppuration. The immediate basal areas of both lungs were comparatively normal. The bronchi showed a moderate congestion with a swollen mucosa, but no exudate; the peribronchial lymph nodes were moderately edematous and the larger bloodvessels had no gross lesions.

Pathologic Histology. The striking features are the prominent interstitial infiltration of cells and the accumulation in the alveoli of large amounts of fibrin and many "Herzfehler" cells. The pleura is normal. The interstitial thickening of the walls is quite diffuse, but in many places the cellular infiltration is heavy enough to assume nodular or seminodular shapes. The background for the hyperplasia often appears to be a collection of fibrin and necrotic material around tiny apertures of bloodvessels.

The predominating cells are medium sized, long or oval-shaped mononuclear cells. They may be designated as epithelioid cells and have little or no cytoplasm. Many of the nuclei are hyperchromatic and take very irregular shapes, *e. g.*, arrow-, club- or comma-shaped. The irregularity of these nuclei is a striking feature. Their presence is associated with necrosis. The alveolar walls are converted into broad irregular strips of fibrin (Fig 7). Weigert stain shows a complete loss of elastic fibers in these swollen alveolar walls. In many places there are large numbers of these epithelioid cells deposited indiscrimately, and again in other places they present a concentric arrangement around small bloodvessels, the lumina of which are partially obliterated. A number of broken-down polymorphonuclears are seen in these infiltrations, especially where necrosis appears. Some large multinucleated giant cells are seen in the large seminodular collections and a few lymphocytes are noted.

The larger vessels show a marked endothelial hyperplasia. Many of the small vessels are partially obliterated by this process.

Other sections emphasize the intense interstitial infiltration collapsing the alveoli, except where they contain some exudate. This is not primarily an atelectasis, in that where the alveoli are maintained by the presence of their contents, their thick walls are shown to excellent advantage. The alveoli contain "Herzfehler" cells, fibrin and the remains of red blood cells. The bronchi are normal.

Summary. This lesion is an inflammatory process in the lung tissue and not passive pulmonary congestion. This will be taken up in the discussion.

Case 4.—M. M., a colored girl, aged 16 years, entered the Presbyterian Hospital March 21, 1927, on the service of Dr. Pemberton. Two years before she had had an attack of acute rheumatic fever with joint pains, precordial pain and hemoptysis. Tonsillectomy was performed in May,

1926, followed by intermittent joint pains. Three weeks before admission she developed an acute polyarthritis, a heavy cough and blood spitting. Temperature on admission was 105° F.; the leukocyte count was 17,300. Physical examination showed an acute pharyngitis and signs of bronchopneumonia, scattered areas of dullness and râles in both lungs, posteriorly. The heart was enlarged and a presystolic murmur was heard at the apex. Death occured on March 28, 1927, due to heart failure. The clinical diagnosis was rheumatic fever and acidosis.

Gross Morbid Anatomy. The heart was markedly dilated. There was an increased amount of pericardial fluid, hemorrhagic and containing fibrin. There was a verrucous valvulitis of the aortic, mitral and tricuspid valves and a fatty degeneration of the myocardium. The left pleural sac contained about 30 cc. and the right pleura 100 cc. of fluid, clear and amber-colored. The pleural surfaces were smooth and glistening. The left lung weighed 650 gm. There was no crepitation, posteriorly, over the lower two-thirds. The color of the lung was mottled, pale pinkish, with irregularly-scattered areas of slate blue, the largest blue area being posteriorly in the lower lobe, measuring 9.5 by 8 cm. These areas contained no air, they were rather leathery in consistency and the cut surface was smooth, glistening and brownish-red in color. In contrast there was an area in the upper lobe, yellowish, granular and solid, presenting the aspect of ordinary lobar pneumonia. There were, in this case, 2 distinct types of consolidation. The right lung weighed 660 gm. It exhibited the same lesions as its fellow, except that the involvement by both the slate-blue and the pneumococcic consolidations were not as extensive.

Pathologic Histology. Section I (from the blue areas of infiltration). The lung tissue is filled with edema. The interalveolar tissues are thickened by a cellular exudate, consisting of irregularly-shaped cells, with solid nuclei, together with broken-down polymorphonuclears and fibrin. There is an occasional very large basophilic monuclear cell and a couple of giant cells are noted. The infiltration is thin but widely diffused. There are many small perivascular collections of cells. There is some peribronchial infiltration by these cells; the other bronchi appear altogether normal. The histology here is not as spectacular as in Cases 1 and 3, but is characteristic. The cellular infiltration is nonsuppurative but consists of cells, the exact copy of which are present in undoubted rheumatic lesions of the myocardium in the same patient.

A section from the yellowish-red, granular consolidation of the upper lobe shows, in contrast, the heavy uniform alveolar exudate of polymorphonuclears and fibrin that characterizes the gray hepatization of lobar pneumonia. The alveolar walls are thin and the capillaries are compressed. There is comparatively no interstitial exudate.

Summary. Acute interstitial rheumatic pneumonitis and pneumococcus pneumonia, involving different lobes of the same lung.

Case 5.—C. Y., a Siamese student, aged 19 years, was admitted to the University Hospital on the service of Dr. Stengel on Febrary 26, 1928. He had an attack of acute rheumatic fever in August, 1927, confining him to bed for 2 weeks. Mitral stenosis subsequently developed. A tonsillectomy was performed in December, 1927. In February, 1928, he had another attack of joint pains, dyspnea, cough and fever. On admission, physical examination revealed an enlarged heart, mitral stenosis and passive congestion of the lungs. The leukocyte count was 19,000. He ran an irregular fever for 2 weeks; had a short remission and then had a prolonged fever; pericardial friction was present from time to time. There was a

progressive downward course and he died on May 9 from cardiac failure. Clinically, the lung signs were interpreted as being due to passive congestion. The necropsy was performed by Dr. Baldwin Lucké.

Gross Morbid Anatomy. Heart: acute pericarditis; recent rheumatic endocarditis of the mitral, aortic and tricuspid valves. Lungs: lobular pneumonia. The gross description by Dr. Lucké is as follows: The left lung weighs 500 gm.; the right, 800 gm. Both organs were of average size and had a very colorful appearance. The basal lobes and areas of the upper lobes are bluish; the others have a pink, still others a dull-red appearance. The basal lobes, particularly in their posterior portions, feel firm. The rest of the tissue had a boggy consistency. Here and there the pleural surfaces, particularly over the basal lobes, were somewhat dull, but there was scarcely any fibrin visible. The cut surface of the basal lobes showed large patches of grayish-brown, bluish and dull red, finely and coarsely granular consolidation, between which lies heavily congested and edematous lung tissue. The consolidations are mostly along the posterior wall and the bronchi have normal caliber. Their mucosa in places was deeply reddened and swollen. Frank pus was nowhere present.

Pathologic Histology. The pleural tissue was prominently thickened, not by superimposed exudate, but by edema, congestion, hemorrhages and a cellular exudate in the subpleural tissue. One notes large, irregularly-shaped cells, occasionally multinucleated. They may streak diffusely through the fibrous tissue, but their perivascular distribution is striking. The subpleural bloodvessels are tremendously dilated and some of them are the seats of hemorrhage. They show a marked hyperplasia of the endothelial lining. The endothelial layer of cells that constitutes the pleural surface is mostly intact. It is broken up in some places and there has been an eruption of fibrin and cells out on the surface.

The lung tissue presents a number of striking features. Although the alveolar walls are slightly thickened throughout by a mild increase in cellularity and edema, their undue prominence is caused by focal perivascular infiltrations, consisting of the large, deeply-stained cells described previously, accompanied by fibrin and endothelial hyperplasia of bloodvessels. These large cells have a basophilic cytoplasm and are often multinuclear. Such larger collections, with the exudative features predominating over the destructive or necrotic, are characteristic of the Aschoff type.

Again one notes the slender, very irregular epithelioid cells often massed in small collections and their long axes radiating from some central point or approaching rosette formation, or again totally irregular in their disposition (Fig. 8). The alveoli are almost universally filled with serum, fibrin and blood.

There are large areas of infarcted tissue, the appearance of which, however, is very different from that of ordinary infarction. While the tissue is flooded with blood and the alveolar lining cells are destroyed, the interstitial tissue is tremendously thickened by fibrin and cellular exudate. These new cells have retained some degree of viability. Many of the nuclei are broken up, but they possess enough staining to indicate that they are the same type of cell seen in the noninfarcted areas. Together with fibrin this exudate has caused tremendous thickening of the alveolar walls in contrast to the skeletal framework left behind in ordinary lung infarction. In and around the infarction, one notes numerous early focal necrotic lesions.

A large bronchial tube is filled with blood; the mucosa is intact. There is no evidence of suppurative inflammation but the capillaries of the submucosa are dilated and there is a rich infiltration throughout the bronchial wall of the perivascular, seminodular, endothelioid exudate seen throughout the lung.

Many of the bloodvessels, large and small, show a tremendous thickening of their walls. (Note: This patient was only 19 years old.) In many, the adventitia and periadventitial tissue are thickened by hyalin fibrosis. Some of them exhibit acute or subacute foci involving one or all three of the vascular layers (Fig. 9).

Some of the larger branches of the pulmonary artery are partially, and others entirely, occluded by what, on superficial examination, might pass for ordinary organization of thrombus; but there is no thrombus, no trace of blood pigment to be seen, and the new intravascular tissue is distinctly inflammatory in type, rather than mere organization. One notes a rather loose edematous collection of fibroblastic tissue, containing many small capillaries, congested and hemorrhagic, surrounded by cellular exudate, large irregular cells, epithelioid cells and lymphocytes.

Summary. This case presented an acute inflammatory process in both lungs—interstitial, perivascular and practically nonsuppurative, with typical Aschoff cells and not associated with inflammatory changes of the bronchial mucosa. On gross inspection, what appeared to be an example of this unusual consolidation, was found to be complicated by infarction. Obliterating rheumatic arteritis contributed to the formation of this infarction.

CASE 6.—W. M. S., a colored girl, aged 17 years, entered the Philadelphia General Hospital on July 9, 1928, with an acute polyarthritis. She gave a vague history of previous attacks of rheumatic fever; salicylate therapy was instituted, but her condition became worse. There was always marked tachycardia, although the joint symptoms subsided temporarily. On August 15 the patient was transferred to the service of Dr. J. C. Small, with a diagnosis of mitral endocarditis, pericarditis and recurring arthritis. Serum therapy was started. The temperature ranged from 98° to 103° F, and the pulse rate was 100 to 170. The white blood cell count was 19,000. The course was progressively downward. On August 22 an impaired percussion note was noted, with diminished breath sounds and some dry râles from the fourth interspace to the base of the right lung. The respiratory rate was 28; the pulse 130 and the temperature 101° F. By August 31 all the signs of rheumatic pneumonitis had vanished. On September 17 and 18, and at later times, there were attacks of auricular paroxysmal tachycardia. On October 2 râles were noted in both lungs, but especially in the right middle lobe and associated with tubular breathing. On October 10 there were signs of consolidation in the lower left lobe. On October 11 bronchial breathing and egophony were heard in both lower lobes, posteriorly. The intensity of the signs in the right lung lessened within two days. Again on October 29 there were signs of consolidation over the lower halves of both lungs. Parotitis and nephritis developed and the patient died on November 4. The clinical diagnoses were rheumatic pancarditis with hepatic congestion, nephritis and bronchopneumonia.

Gross Morbid Anatomy. The autopsy (Dr. E. Weiss) revealed a subacute and chronic adhesive pericarditis. The valve structures were apparently normal.

The description of the lungs is as follows: "The right lung weighs 460 gm. The upper lobe is voluminous and pinkish-red in color. The lower lobe is smaller, firm and almost entirely solidified. On section it is dark red in color, with areas that are granular in appearance and resembling bronchopneumonia of some duration." We examined these lungs through the kindness of Dr. Weiss and found that the lower lobes were solid, dark red

in color, and in many areas showed a very thin fibrinous dulling of the pleural surface. On section there was noted a consolidation with a finely-granular surface, dark red in color and of rubbery consistency. There were also small, grayish-red, firm areas and granular, apparently bronchopneumonic, although no fluid pus was noted. There was no suppuration in the bronchial tree.

Pathologic Histology. The pleura is moderately thickened by a fibrosis; the subpleural capillaries are congested. The pulmonary lesion is not uniform. In some fields the alveoli are partially aërated and contain small or moderate numbers of erythrocytes. Their intra-alveolar walls are thickened by congestion and small isolated groups of endothelial cells. Epithelioid cells and smaller round cells are noted. The striking features are large foci scattered throughout the section, superficially resembling abscess formations (Fig. 10), nodular and some so large as to nearly occupy the entire low-power microscopic field. Others are much smaller, occupying an area the size of one or two alveolar spaces. They do not have regular contour. In some places a tendency to demarcation is present, but it soon is lost in a gradual extension into the surrounding lung tissue by infiltration along thickened alveolar walls and by gradually thinning out in various directions. Other areas show lung tissue consolidated by tremendous outpouring of red blood cells and fibrin into the alveoli. The cellular exudate within the alveoli is scanty except where the interstitial infiltration has heaped up and "poured" out into the alveoli, through broken-down walls. Marked fibrinous thickening and degeneration of alveolar walls is notable. In some places this fibrinous infiltration is so marked and homogeneous, accompanied by occlusion or obscuration of the capillary, that the alveolar walls have the appearance of strips of ribbon (Fig. 11).

The interstitial cellular infiltration is the same as noted in previous cases, except that the nodule formation assumes unusual prominence, equivalent to or greater than that seen in the great majority of acutely rheumatic hearts. These focal lesions are of various sizes, ranging from the very small but definite Aschoff collections (Figs. 11, 12 and 13) to the very large lesion that occupies the larger part of microscopic fields. The large nodules consist of densely-packed endothelioid cells, polymorphonuclears, round cells and detritus. Many cells apparently have broken up and the original lung tissue has been replaced by a background of fibrin. The picture is very suggestive of an acute granulomatous lesion. It was seen grossly as a small grayish-red nodule and was then interpreted as being an indurated or "chronic" bronchopneumonia. In one field a bronchial branch is seen partially filled with this cellular exudate, which is an extension of a large adjacent nodule. This appears to be an infiltration of a bronchiolar wall with local destruction. The remaining portion of the wall presents a normal appearance. The smaller nodules are typical rheumatic lesions, containing the various cellular elements that have been described. The giant cells with two to three nuclei are seen in most of the nodules. Polymorphonuclears, while numerous in the large granulomatous lesions, are relatively few in the smaller collections and the diffuse interstitial exudate. The bloodvessels show the same adventitial and medial infiltrations as seen in the previous cases.

Summary. Acute interstitial rheumatic pneumonia.

Case 7.—R. S., a white girl, aged 17 years, was admitted to the Philadelphia General Hospital on the medical service of Dr. A. A. Stevens, with soreness over the entire body. The patient was a normal child until 3 years ago, when, at the age of 13 years, she had an acute illness characterized by fever, chills, sore throat, excessive sweats and pain in all joints of the body.

She was confined to bed for several weeks. When she recovered from this acute attack she was left in a very nervous state and frequently had twitching of various parts of the body. The diagnosis was St. Vitus' dance.

Six weeks ago, while coming from Scotland, she began to feel badly and to have slight sore throat; twitching continued intermittently. Three weeks ago she was again forced to bed with chills and fever and a severe sore throat. She again noticed pain and stiffness in her neck, followed in a few days by pain in both knees, both ankles and right shoulder. She has been very short of breath since the onset 3 weeks ago.

Physical examination showed the presence of a severely toxic infection. The heart was considerably enlarged; a presystolic rumble, a harsh mitral murmur and irregular rhythm were noted. The latter varied between a flutter and a fibrillation of the auricles. A mild icterus was present. The white blood cell count was 13,900. The blood culture was sterile. Diarrhea became a troublesome symptom. Progressive cardiac enlargement was noted, followed by hepatic and splenic enlargement. Two days before death the patient complained of great pain over the precordium and in the right chest. Apparently no physical signs were elicited; the critical condition of the patient prevented a more adequate examination.

Gross Morbid Anatomy. Autopsy (Dr. G. Robson): Gross anatomical diagnoses were: obliterative pericarditis; chronic mitral and aortic endocarditis (rheumatic); pneumonia (rheumatic type) of the right lung. Dr. Robson's gross description of the lungs is as follows: "The left lung weighs 365 gm. The pleural surfaces were normal. The lung is crepitant throughout and on section the surface is not excessively bloody. A few small reddish areas of solid consistency are present in the lower lobe. The right lung weighs 590 gm. A large portion of the lower and a small part of the upper lobe were consolidated. On section these portions of the lung have a reddish, fleshy appearance and were nonair-containing. The appearance, while resembling atelectasis, does not seem to involve collapse of the lung and suggests some type of acute pneumonitis."

Pathologic Histology. A section from the right lower lobe shows a consolidation of the lung tissue. The pleura is not included. Most of the consolidation is caused by the filling of the alveoli with serum, fibrin and hemorrhage. Many of the alveoli contain no cellular infiltration or very few cells, there being an occasional phagocyte and desquamated epithelial cell. In many areas the alveolar hemorrhage is marked. In contrast to the slight cellular infiltration in the alveoli, one notes an undue cellularity in the alveolar walls, variable in intensity. It is moderate throughout most of the section, consisting of small collections of very irregular, usually oval or comma-shaped, medium-sized and deeply-staining cells, often in and around a necrotic area with a background of fibrin. Many of these small groups of cells are collected around congested capillaries. There are in addition large areas densely cellular, so that in lower magnifications the original lung architecture is made out with difficulty. One of these larger infiltrations is perivascular, spreading from a large branch of the pulmonary artery, out into the surrounding lung tissue in an interstitial manner, but the alveolar walls are so thickened by the new cells and by edema that the alveolar spaces are often compressed or collapsed.

The type of cell has been described: irregular, elongated, deeply staining, with little or no cytoplasm and accompanied by small, round cells and occasional polymorphonuclears. A few large hyperchromatic cells are present, but the multinuclear giant cells are not seen.

The bronchi show no definite change. The larger bloodvessels show a surrounding zone of edema, invaded by numbers of the new cells. A few alveoli, three or four, are densely packed with polymorphonuclears.

Summary. Interstitial rheumatic pneumonia.

CASE 8.—B. D., a white woman, aged 48 years, was admitted to the medical service of the Philadelphia General Hospital on July 5, 1928 with the complaint of pain and swelling in the ankles and wrists. The onset occurred 2 weeks before with pain in the metatarsal joints. On June 28 the ankles were involved, and on July 4 the left wrist and fingers were swollen and painful. Fever and anorexia accompanied the arthropathy. The past medical history consisted of measles in childhood, anemia from the age of 15 to 20 years and influenza in 1918; since that time there have been repeated attacks of tonsillitis. Dyspnea, palpitation and occasional edema of the ankles have been noted as transient attacks for the past few years. There has been no previous history of rheumatic fever and no history of precordial or chest pain. One sister had many attacks of rheumatic fever. Three children died in early years of infection, apparently unrelated to rheumatic fever.

Physical examination on July 5 showed a painful swelling of many of the larger joints, particularly the wrists and ankles, making movement impossible. She had a fever of 101° F. and a pulse rate of 100. The tonsils were enlarged and infected. Marked venous pulsation was seen in the neck. Lung examination was negative. The heart was enlarged, especially to the left; the rhythm was regular and a rough systolic murmur was heard at the base. Treatment was followed by no definite improvement. On July 13 a cardiac irregularity developed. July 18 the patient was transferred to Dr. Small's rheumatic fever service. A consolidation, as indicated by bronchial breathing and dullness, was found in the base of the right lung. Serum therapy was tried, but without avail. Fibrillation, cyanosis and abdominal distention developed and the patient died on July 23. Laboratory data: Red blood cells, 3,700,000; with blood cells, 17,000; hemoglobin, 3.2 gm. A throat culture was positive for streptococcus cardioarthritidis. Blood culture was negative; blood urea nitrogen, 16.

Gross Morbid Anatomy (Dr. Konzelman). The heart weighed 790 gm. and presented a typical rheumatic pancarditis. The aortic valve was stiffened by previous disease and a recent verrucous endocarditis. The left lung weighed 390 gm. and the right, 650 gm. The lesions were much the same in both lungs but more pronounced in the right. The upper lobes were grayish mottled by black carbon deposit. The apical portions and the anterior edge seemed overdistended and paler. The remaining part of each lung was a bluish-red and at the base appeared slightly depressed. The entire lower lobes were a deep blue. Subserous petechiæ were scattered over the entire surface and a few dark pea-sized nodules were seen on the pleural surface. Section shows the upper lobes to be gray and crepitant while the lower lobes were dark red and airless. The bronchial mucosa was pale red and smooth. Diagnosis: interstitial pneumonia.

Pathologic Histology. There was an acute and subacute interstitial pneumonitis accompanied by marked capillary congestion. The cellular infiltration was similar to those described in the preceding cases, except that it was more uniform and without the presence of distinct nodular formation. There was no polymorphonuclear invasion. In many places the alveolar walls were markedly thickened. The diminution in alveolar space might be interpreted as a partial atelectasis, but the pneumonitis was the predominant change. In the same fields many of the alveoli were distended by hemorrhage or edema, but no exudate.

CASE 9.—R. I., a young white male, aged 26 years, was admitted January 13, 1931, to the Jewish Hospital on the medical service of Dr. E. I. Becker, with a diagnosis of lobar pneumonia and empyema. He died on January 16, 1931. One month before he felt chilly and then feverish. Soon afterward he had several drenching sweats and at the same time began to cough up a brownish sputum. With every cough there was a sharp pain

in the right side of the chest. This pain and expectoration gradually abated. For 2 weeks he had been moderately jaundiced. On January 12 he became extremely short of breath and his fever, which had been irregular and decreasing, reappeared. He was admitted to the hospital on the following day. He never had a sore throat and there was no joint inflammation in this attack.

At the age of 8 years he had an attack of rheumatic fever. Five years before admission he was treated in another hospital for cardiac disease. For many years he has been somewhat short of breath.

Physical examination revealed moderate jaundice. Respiration was rapid and shallow. Examination revealed a flat percussion note from the right base up to the fifth rib and an impairment from that level to the second interspace. The breath sounds over the right lower lobe were distant and tubular. The left side was resonant and a few coarse râles were heard over the entire chest. The heart was much enlarged, both to the left and right. Thrills were palpable over the aortic area and the whole right parasternal region, and to some extent at the apex. Blowing murmurs were heard at both the mitral and aortic areas.

The patient was obviously too ill for detailed examination. He was perspiring freely; cough was not frequent and it was unproductive. He had no chill since the first part of his illness 1 month ago. His temperature, which on admission was 101° F., fluctuated between 98° and 102° F.; the pulse rate was 110 to 160 and the respiratory rate was 28 to 40. On January 14 his condition appeared to be improved; marked impairment was limited to the right lower lobe and the temperature was normal. Roentgen ray examination on this date showed "a consolidation at the right root and base, with a probable plastic pleurisy along the lateral aspect of the chest. There is no distinct evidence of fluid in the pleural cavity and, if present, is very scant. The left lung is clear." On January 16 some elevation of fever was noted. The physical signs in the right lower lobe remained unaltered except for complete loss of breath sounds; râles, previously infrequent, were heard over the entire right lung and a few at the left base, where percussion was moderately impaired. Later, on that day, the patient became extremely dyspneic and cyanotic. Oxygen and stimulation did not help and death occurred rather quickly in a patient who on the previous day had shown considerable clinical improvement.

On January 13, 1931, hemoglobin was 74 per cent; red blood cells, 4,000,000; white blood cells, 18,000; neutrophils, 86 per cent; blood sugar, 0.125; blood urea, 20; blood culture was negative; sputum cultures, none (patient scarcely coughed).

Gross Morbid Anatomy. Acute mediastinitis, involving the mediastinal pleuræ and exopericardium, rheumatic pancarditis and widespread bilateral pneumonia were the salient features. The heart weighed 700 gm. and exhibited an acute fibrinous pericarditis over the base. The hypertrophy was due to stenosis of the aortic, mitral and tricuspid valves.

The spleen was enlarged, blackish-red and firm. It did not possess the pulp hyperplasia of ordinary pneumonia. The liver was partially destroyed by a severe passive congestion.

The left lung weighed 800 gm.; it was moderately enlarged. The upper lobe was aërated, gray in color, but spotted by foci of hemorrhage. The lower lobe was consolidated and dark red in color. Section showed this lobe to be entirely solidified, dark reddish-brown with occasional fine grayish markings suggestive of interstitial thickening. The granularity was very fine and in some areas was lost. The lobe was moderately larger than normal. There was no sign of suppuration. The bronchial tree was moderately congested but showed no distinct inflammatory reaction. The upper lobe was emphysematous and congested.

The right lung was consolidated in all three lobes. It weighed 1100 gm. and was moderately enlarged. It was dark reddish-blue and slate-colored. Over the lateral aspect of the lower lobe was a fibrinous hemorrhagic pleuritis. Section showed a complete solidification, dark reddish, with an almost smooth surface, fleshy and suggestive of the appearance of firm, deeply congested splenic tissue. Some areas were rusty-brown in color. Fine grayish markings were seen occasionally as in the other lung, and the bronchi presented the same negative findings. The lymph nodes were dark and moderately edematous. Examination of the pulmonary artery showed throughout both lungs an extreme degree of atheromatous degeneration. In the lower part of the right upper lobe there was a recent infarction. Section showed a laminated grayish occlusion of the arterial branch at the apex of the infarction. The appearance was suggestive of arteritis and thrombosis. All bacteriologic studies at necropsy were negative.

Pathologic Histology. The pleura in numerous sections show a slight thickening, due to a moderate subpleural edema. There is no acute inflammatory reaction, except over an infarction, where the endothelium has been disrupted and a thin layer of fibrin deposited.

The alveoli are filled with masses of red blood cells and fibrin. In some places there has been apparently a rupture of the alveolar wall followed by an overflow of blood. Practically every alveolus is involved. The lining epithelium is swollen and partially desquamated. Only an occasional white blood cell is seen in the alveolar contents. The notable exception to this is the presence of large numbers of pigment-laden phagocytes in some alveoli. In contrast to the character of the alveolar exudate the interstitial tissue (interalveolar walls) is remarkably thickened. This change is seen throughout all fields, varying only in degree. Capillary congestion and hemorrhage and endothelial hyperplasia are seen in the least affected areas. The more frequent changes are a focal and also in many fields, a diffuse cellular infiltration of epithelioid cells, round cells and an occasional polymorphonuclear. The number, dark staining and the irregular shape of the epithelioid cells are striking. Often they appear to be fragmented. Fibrin is present in large amounts; some of the alveolar walls are represented by broad strips of fibrin, in which are found numbers of epithelioid or fragmented cells. In such places a severe grade of necrosis is evident. Weigert stain shows marked destruction of elastic tissue. Small nodular foci are scattered throughout; in some fields they have broken through the alveolar wall, projecting in bulbous collections into the alveolar space. Occasionally large nodules of the same type are found which obliterate two or even many alveolar spaces. A few nodular thickenings contain the larger Aschoff cells, including small giant cells with two or even three nuclei.

Sections through the infarct of the right upper lobe show that the widespread interstitial and nodular infiltrations have not been entirely destroyed by the ischemia and are easily recognized at the periphery of the infarction. Large and small branches of the pulmonary artery are completely filled or their lumina reduced to small channels by an edematous granulation tissue. Other vessels show an acute arteritis and thrombus. One large branch in longitudinal section shows a large portion destroyed by an acute, dense cellular infiltration that extends through the entire wall and fills a part of the lumen. The structure of the original three vascular layers, including all of the elastic tissue has been destroyed. Another vessel, where the inflammatory process is less advanced, is dilated and its thin wall is diffusely invaded by epithelioid cells such as are seen in the lung parenchyma; a large sector of the media is destroyed and replaced by fibrin. The thrombus is invaded by epithelioid and round cells. Another large vessel, which was partially occluded by granulation tissue apparently the result of a previous

inflammation, is heavily infiltrated by the same acute cellular process that was found in the lung tissue, the mediastinum and heart of the patient. All normal structure in this vessel, except a fibrous adventitia, has been obliterated. It appears that an acute recurring arteritis of specific rheumatic type, is responsible for the infarction.

Outside of the infarcted area the smaller vessels all have some degree of thickening. The adventitia, particularly, shows an excess of hyaline fibrosis. Many contain small foci of acute inflammation and necrosis in the media. The arterioles show an endothelial hyperplasia, often to the point of occlusion. The profusion of interstitial fibrin and infiltration often obscures the capillary structure. In many places the latter has disappeared.

The bronchioles are often filled with blood and fibrin. Their walls may be thickened by congestion and edema. At some points there is noted a rupture of the wall with extrusion of the interstitial fibrinous exudate, often laden with phagocytes. In the larger branches the mucosa is intact and no intrabronchial pathology is evident.

Summary. Rheumatic lobar pneumonia, involving the entire right lung and left lower lobe. There was a history of pneumonia and pleuritis at the beginning of this patient's last illness one month before. The final lung changes apparently represent a recurring attack.

Discussion. The term "rheumatic pneumonia" present in old medical literature, has been practically forgotten in the last half century. The tendency to precision in medical thought and nomenclature caused "rheumatic pneumonia" to follow "typho-malaria" and other dubious terms into the discard. Until a few years ago "rheumatic fever" meant essentially acute arthritis and endocarditis. Today a widespread involvement of many tissues is recognized. The advance is due in most part to the recognition of a specific pathology, which began with Aschoff's description of submiliary nodules in the heart.[18] At the present time identification of a rheumatic lesion depends on histology; the presence of focal perivascular lesions, necrotic and proliferative of the Aschoff type, is the criterion for diagnosis. Recently there has been considerable discussion as to specificity of the Aschoff lesions for rheumatic fever. While something similar is apparently produced in experimental animals by the injection of many strains of nonhemolytic and possibly hemolytic streptococci, it is seen in human pathology preeminently in rheumatic fever and we consider it characteristic in the cardiac lesions of that disease.

This series of cases was chosen from a large number of rheumatic fatalities, because it represents a small group of patients dying in the acute stage of the disease, who presented definite pulmonary signs, usually of consolidation. Many other patients having the same clinical picture, but surviving after a stormy course, have been seen in the last four years. Other cases, similar to those included in this report, have been observed at necropsy, but for various reasons could not be included in the pathologic study. A large number of rheumatic deaths presented the characteristic find-

ings of subacute and subchronic pleuritis with effusion and basal atelectasis. They do not fall within the scope of this report, apparently representing a later stage of rheumatic pulmonary disease and often complicated by cardiac failure. One such case included in this series (Case 2, F.R.) clinically presented pleurisy, cardiac failure and atelectasis, and at necropsy, isolated foci of pneumonitis without consolidation.

In our study the gross and histologic examinations revealed pulmonary changes which apparently had not been previously described. They were presented at the December meeting of the Pathological Society of Philadelphia, 1927, and published in an abstract in the *Archives of Pathology*, 1928.[16] It was therefore, with great interest that we read the paper on the "Rheumatic Lung," by A. E. Naish[17] whose findings are identical with our own.

The acute pulmonary lesion of rheumatic fever, rheumatic pneumonia or pneumonitis, is an acute interstitial inflammation, having as its basis the vascular damage and perivascular infiltrations that are common to all acute rheumatic lesions. It is practically nonsuppurative, thus differing from the acute interstitial pneumonias caused by hemolytic streptococci, such as are associated with epidemic influenza[19] or the bronchopneumonia of measles.[20] In none of our 9 cases was there any considerable exudate of polymorphonuclear cells. In the most acute stages, characterized especially by necrosis, one sees groups of polymorphonuclears, scanty in number and sharing in the karyorrhexis suffered by all cells in these areas of acute focal necrosis. The nonsuppurative character of this inflammation precludes the development of pyogenic changes, such as gray hepatization, abscess or empyema, except through the medium of secondary infection.

Consolidation was present in 8 of these cases and did not seem to show a preference for one lung over the other. Both lungs were involved and usually to about the same extent. In Case 4 (M.M.) the left lung showed a greater involvement than the right lung. In Case 9 (R.I.) 4 lobes were consolidated, including the entire right lung. The largest consolidations were in the lower lobes with smaller infiltrations in the upper lobes, especially toward the hilum and along the interlobar fissure. Although an entire lower lobe was often involved, consolidation was not as bulky as in lobar pneumonia. The rheumatic lesion's color, varying from dark blue to a rusty-brown, and the delicate white tracery under the pleura, due to interstitial exudate, and its appearance on section, are distinct features. The dark red, firm finely-granular, slightly moist cut surface, doubtless led to its description as a "splenization." Naish points out its resemblance to solid India rubber. It is not atelectasis. The physical signs elicited in the examination of the lungs of acutely ill rheumatic fever patients, have often been attributed to atelectasis. It was noted in only 1 of these 9 cases (Case 2, F.R.)

where there was no consolidation, but basal collapse associated with subacute and chronic pleuritis. Basal collapse, sometimes to an unusual degree, and often accompanied by gelatinous edematous pleural adhesions, is seen frequently in subacute aspects of the disease. Our belief is that the lesion described in this report is either independent of those changes or, in more probability, precedes them.

We would speak of this lesion as pneumonia or pneumonitis, depending upon its extent. Small hemorrhagic foci, with little or no cellular infiltration, often seen in the nonconsolidated lobes of these cases and indeed in many cases of rheumatic fever with virtually no pulmonary involvement, scarcely merit the title of pneumonia or of "hemorrhagic lobular pneumonia." However, if the presence of inflammatory consolidation with the subsequent alteration of physical signs warrants the use of the term "pneumonia," the lesions in 8 of the cases in this series can well be called "rheumatic pneumonia." As a fine distinction, in contrast to the ordinary bronchopneumonia, this consolidation could possibly be termed "perivascular pneumonia."

Histologic examination gives definite proof of the identity of the lesion. This brings up the point as to what is the characteristic microscopic picture of a rheumatic focus. Evidently, as stated in the protocol of the first case, the cellular complexion of these lesions differs in different locations. The difference seems to depend on the age of the lesion and to a lesser degree in consideration of the disease in general, on the organ that is involved. The areas of acute focal necrosis, small perivascular groups of broken-up polymorphonuclears and slender irregular epithelioid cells might conceivably be the first of a number of phases of inflammatory reaction and to be followed later by a more proliferative process, the Aschoff "nodule." This more mature stage of the reaction is characteristic and its presence establishes the diagnosis of rheumatic fever. It is this interstitial perivascular infiltration of large cells, often multinucleated, that is a significant part of the histologic picture in rheumatic pneumonitis.

A third phase of this reaction is suggested by the presence of fairly large cells, with solid irregular nuclei replacing the large Aschoff cells and giving the impression that such a lesion is a subacute one, verging on early sclerosis.

Another important feature is the vascular destruction that is usually seen in rheumatic pathology—the endothelial hyperplasia, the rupture of capillaries with hemorrhage and the liberation of fibrin. Although the condition is primarily interstitial, this heavy infiltration of blood and fibrin "pours" over into the alveolar spaces, lending bulk and the various color changes to the gross morbid appearance. It is often intense and in striking contrast to the few cells within the air sacs. The consolidation is the interstitial

exudate, plus this alveolar hemorrhage. Occasionally one may see small areas of hemorrhage with comparatively little or no cellular exudate and surrounded by air-containing tissue. Grossly these will appear as hemorrhagic foci without consolidation. They are apparently identical with the small hemorrhagic lesions described by Paul. Many of them show an inflammatory aspect, perhaps a few irregular epithelioid cells or an occasional small perivascular group. We would consider them to be a very mild, but definite expression of acute rheumatic pulmonary pathology.

Where phagocytosis of hemorrhage occurs, as evidenced by the appearance of large phagocytic monocytes, so-called "Herzfehler" cells, one may be confused as to whether there is a true inflammatory process or only passive congestion, especially since there may be coëxisting mitral stenosis. Case 3 (E.H.) in this connection is worthy of comment. The gross appearance of the lungs was certainly not that of passive congestion. The lesions were too localized; large portions of the lung tissue were comparatively anemic and the bases were fairly clear. The cellular infiltration was, of course, distinctly inflammatory, including large Aschoff cells. The presence of "Herzfehler" phagocytes must then be explained by the hemorrhagic character of the inflammation, which in acute rheumatic lesions is not uncommon and in this particular lesion, acute pneumonitis, is rather characteristic.

The above changes are the result of vascular damage in small bloodvessels—capillaries and arterioles. Endothelial hyperplasia to the point of complete occlusion of these small vessels, is now a recognized step in the development of a rheumatic lesion. The knowledge of vascular changes in this disease has recently been advanced by the recognition of intimal changes in the aorta and other large bloodvessels.[21] Obliteration by the inflammatory process of a large artery, contributing to the formation of gross infarction, has not to our knowledge been previously described. Sudden occlusion of a large coronary artery in the course of rheumatic fever in a patient who recovered has been recently recorded. Such occurrence is rare.[22]

In Case 5 (S.C.) and Case 9 (R.I.) large branches of the pulmonary artery were completely occluded by tissue that is distinctly inflammatory, identical with perivascular infiltration, which has spread through the vessel wall to reach the intimal surface. The intravascular infiltration exhibits numerous new capillaries and perivascular collections of endothelioid cells. There is presented, therefore, vascular occlusion by rheumatic arteritis with destruction of large areas of tissue, in contrast to a similar microscopic process that is going on constantly in the small bloodvessels in rheumatic fever. The development of infarction was aided, of course, by cardiac weakness which embarrassed the collateral circulation.

Inflammation of the trachea and bronchi was not noted in these cases. At least there was an absence of purulent changes in the

mucosa. The occasional reddening and swelling of the mucosa can be explained by the microscopic picture of peribronchial and intrabronchial infiltration of cells, which are probably transported there by the lymphatics draining the pulmonary tissue. Sometimes the smaller bronchial branches were filled with blood. The rather mild changes in the bronchial tubes and the absence of gross lesions in the trachea, will lend some significance to the statements of clinicians that the pulmonary involvement in rheumatic fever, unlike bronchopneumonia, is not a result of upper respiratory tract infection. Rheumatic pneumonia, however, may be associated with other infections. Case 4 developed a rheumatic pneumonitis and a pneumococcic lobar pneumonia.

Singularly enough, the majority of these acutely inflamed lungs showed but few lesions of their pleural surfaces. There was occasionally a very mild dullness of an otherwise smooth surface. Small amounts of clear fluid were recovered from the pleural sacs. In Case 2 (F.R.) an exception as regards the pleural involvement was an adhesive pleuritis and mediastinitis, without consolidation of the lung tissue.

Eight of these cases exhibited a pericarditis. Case 2 (F.R.), without the consolidation, had a pericarditis; Case 3 (E.H.) on the contrary showed no pericarditis, but did have massive consolidation. Rheumatic pneumonitis and pericarditis usually coëxist, but apparently need not always do so. All the subjects had some acute manifestation of cardiac rheumatism; all but 1 (Case 6, W.S.) had acute endocarditis.

The endothelioid reaction that is an essential feature in rheumatic pneumonitis is seen, as far as we know, in only one other condition in human pathology, and that is occasionally in subacute bacterial endocarditis. The histologist may, in such cases, find small perivascular groups of large cells, but that is only a trivial microscopic suggestion of what in rheumatic fever may proceed as far as the production of lobar consolidations. Ninety per cent of cases of subacute bacterial endocarditis show implantation of that condition on rheumatic carditis. Histologic changes in the lungs of such patients, therefore, may well be part of a rheumatic pathology. Experimentally this endothelioid reaction in lung tissue is seen constantly in rabbits following injections of the Streptococcus cardioarthritidis.[23] The gross appearance of rheumatic pneumonia (Fig. 1) bears a close resemblance to lungs consolidated in the course of Streptococcus viridans infection in young children. The histology of the latter infection likewise is suggestive, in some ways, of what is seen in rheumatic fever. Incidentally the presence of such an inflammatory reaction in lung tissue, in human pathology, disproves the contention that the endothelioid cells of the Aschoff nodule in heart muscle, are derived from muscle cells.[24]

Summary. Nine cases of acute rheumatic fever are presented with reference to their pulmonary pathology. Eight of these show

an acute inflammation of lung tissue with consolidation; the ninth shows pleurisy with subacute lung involvement. All of them are associated with acute rheumatic heart disease. The inflammatory pulmonary reaction consists of an interstitial perivascular exudate of large endothelioid cells, identical in morphology with those found in rheumatic heart lesions and considered pathognomonic of rheumatic fever. Hemorrhage and fibrinous exudate are prominent features. We therefore consider that in many virulent cases a characteristic rheumatic pneumonia is to be found.

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ABDOMINAL CRISES IN SICKLE-CELL ANEMIA.

By Frank E. Leivy, M.D.,

ASSISTANT PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL; INSTRUCTOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

Truman G. Schnabel, M.D.,

PHYSICIAN PHILADELPHIA GENERAL HOSPITAL; ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

(From the Medical Division of the Philadelphia General Hospital, Philadelphia, Pa.)

In 1910 Herrick described peculiar poikilocytes which he found in the blood of an anemic negro. He applied the descriptive term sickle to these cells. Only 3 instances[4,5,6] of this sickling phenom-

enon were observed and reported in the next 13 years. In 1923, however, with the appearance of papers by Sydenstricker[2] and Huck[3] sickle-cell anemia was established[1] as a definite disease entity. Since this year an ever increasing number of articles in the literature has served to acquaint the medical profession with the general pattern of this malady. The articles of Emmel,[7] Graham,[8,9] Hahn,[10,11] Josephs,[12] Rich,[13] Moore,[14] Anderson,[15] and that of Landon and Lyman[16] are especially noteworthy in this respect. With this array of available information set forth, there seems to be no need for our purposes to redraw the picture currently thought to represent sickle-cell anemia. In spite of the excellent observations made and reported, many features of this fascinating disease remain unexplained. Among these are the so-called abdominal crises experienced by some patients whose blood reveals sickle cells.

Recurrent abdominal pain is emphasized by all writers on sickle-cell anemia. Epigastric pain after eating and recurrent attacks of epigastric and left hypochrondriac pain are noted in all reported protocols. Such episodes occur not infrequently during the disease's latent phase when the symptoms are few and the physical signs are only suggestive. During the active phase these attacks may occur more frequently and may be very severe. Vomiting may occur. In addition one may find at the same time some degree of abdominal tenderness with rigidity, fever and leukocytosis. Not infrequently the attacks simulate those occurring in the tabetic. This simulation is accentuated by the presence of leg ulcers and lymphadenopathy. The symptoms may be general, unilateral and upper or lower abdominal in location. The attacks may be acute enough to simulate gall stone colic, appendicitis, or a ruptured viscus and the need for an emergency laparotomy may seem to be imperative. The sickle-cell anemic patient may of course be the victim of such abdominal diseases; on the other hand, the surgeon may be disappointed in not finding an explanation for the patient's difficulties at the time of operation. It is not unlikely that sickle-cell patients have been subjected to needless laparotomies. Such experiences are not generally reported, due to the natural tendency not to publish diagnostic failures especially when the correct diagnoses have not been established. It is quite possible to miss mild degrees of sickling in the usual blood studies as they are made, especially when these have been limited to leukocytic counts. Graham's[8] case had an appendectomy performed on a previous admission. One of Alden's[17] cases was diagnosed either pneumonia or appendicitis, but fortunately the condition subsided before operation was performed. Hein's[22] patient sought relief for epigastric pain. Smith's[18] case presented symptoms suggestive of gall bladder disease with complicating appendicitis. The discovery of sickle cells in this patient's blood obviated the need for operative intervention. We have observed a patient who would undoubtedly have been

subjected to an abdominal operation but for the knowledge that his blood contained sickle cells. Two other patients with painful abdominal attacks are cited so that certain matters pertaining to the occurrence of abdominal crises in the course of sickle-cell anemia may be conveniently discussed.

Case Reports. CASE 1.—A male negro, aged 25 years, was first admitted to the Philadelphia General Hospital in October, 1926, because of severe pains in his arms and legs. A diagnosis of subperiosteal abscess of the right tibia was made, and the lesion was incised and drained. A culture of the puslike material obtained was sterile. The patient made an uneventful recovery and eloped from the hospital before the wound had completely healed.

In September, 1929, he was admitted for the second time because of pain in his legs and back. An attempt was then made to establish a diagnosis of congenital lues despite negative serologic findings in both the blood and spinal fluid. It was further noticed that he presented the picture of a hypopituitary disturbance. This suspicion was strengthened by an increased sugar tolerance and the findings on Roentgen ray examination of a sella turcica larger than normal with hazy and probably rarefied posterior clinoids. The basal metabolic rate was + 4 per cent, and the visual fields were normal. On discharge the final diagnoses were congenital lues with luetic periostitis and aortitis, congenital psychopathic inferiority, and hypopituitarism.

On January 1, 1930, the patient was admitted for the third time, complaining of severe pain in both shoulders and lumbar spine, and occasional vomiting and pains in the epigastrium after eating. This was the first time the patient was seen by us.

Physical Examination. The patient was a black male, aged 25 years, who appeared much younger, and distinctly under normal size. There were few positive findings. The tonsils were hypertrophied and diseased. The heart was enlarged to the left and right and a systolic murmur of moderate intensity was heard at the apex and at the first intercostal space to the right of the sternum. The blood pressure was 110 systolic and 62 diastolic in both arms. The extremities revealed a scar over the right tibia, the patient showed tenderness over both deltoid muscles, and exaggerated reflexes. The posterior and anterior cervical, the epitrochlear and inguinal glands were uniformly enlarged.

Laboratory Observations. The red blood cells varied from 2,400,000 to 3,300,000; hemoglobin 60 per cent to 80 per cent. The color index was + 1. The white blood cells varied from 10,900 to 19,400; the differential count was normal. Forty-four nucleated red blood cells were seen in counting 100 white blood cells. Anisocytosis, poikilocytosis, and polychromatophilia were found routinely. Sickle cells varied from 6 to 50 per cent in both the fresh preparations and the stained films. Reticulocytes varied from less than 1 to 5 per cent. Clotting time was 2½ minutes and bleeding time 3 minutes. The platelets varied from 280,000 to 480,000. Hemolysis began at 0.30 per cent and was complete at 0.20 per cent salt solution. The blood sugar was 80 mg., blood urea nitrogen 12 mg., cholesterol 165 mg., calcium 10.4 mg., phosphorus 4.6 mg. per 100 cc. of blood, and blood pH was 7.44. The icterus index varied from 8 to 15; the Van den Bergh reaction was delayed. The urine showed a constant trace of albumin; the specific gravity varied from 1006 to 1008; urobilin was present; and 70 per cent elimination of phenolsulphonephthalein occurred in 2 hours. Gastric analysis on one occasion showed a free hydrochloric acid of 6; total acidity of 18; on another occasion 25 free and 60 total in terms of $\frac{1}{10}$ normal NaOH solution.

Roentgenologic Examination. The gall bladder was found normal by the intravenous dye test. Gastrointestinal Roentgen ray study showed no abnormalities except for increased colonic peristalsis. The heart was enlarged to the left and there was a considerable enlargement of the right auricle. The aorta was normal.

Skull. There was considerable thickening of the outer table of the parietal bone. This was due to new bone formation, showing as striations perpendicular to the long axis of the skull. The suture lines were indistinct.

Spine. The vertebræ were shortened in their vertical dimensions and somewhat widened in diameter. They had a soft appearance, there being considerable decalcification. The trabeculæ were rather prominent and sharp and the cancellous spaces were rather large. (Fig. 1.)

Pelvis. The bones of the pelvis showed considerable osteoporosis. The trabeculæ were rather sharp.

Ribs. The ribs were irregularly deformed. They had a soft appearance due to an osteoporosis. The cancellous structure was rather prominent. The scapulæ were apparently not involved. The inner portion of the clavicles showed osteoporosis.

Left Foot. There was considerable osteoporosis. The trabeculæ were sharp and had a pencilled appearance. There were a number of dense lines of bone condensation extending across the medullary cavity. These were particularly prominent in the lower end of the tibia. The cancellous spaces were rather large. (Fig. 2.)

The changes noted in the skull and the other bones were characteristic of the osseous lesions found in sickle-cell anemia.

Course. On many occasions during the patient's long stay at the hospital he was seized with severe abdominal pain, at times localized in the upper quadrants and at other times in the lower quadrants. These critical attacks were accompanied by nausea, vomiting, rigidity, diminution of peristaltic sounds, and generally with fever up to 102° F. The agony was so excruciating that the patient assumed all kinds of bizarre positions, at times extreme opisthotonos. Frequently these attacks were accompanied by pain in the back, thighs or lower chest. Morphin sulphate in large doses at short intervals was necessary for relief of the pain. Diagnosis of appendicitis, cholecystitis, pancreatitis, peritonitis and Pott's disease were made by those who saw him during attacks. Surgeons who were consulted advised against operation on a number of occasions, chiefly because of the sickle-cell features observed in the patient.

Case 2.—A colored girl, aged 23 years, was admitted to the Philadelphia General Hospital on September 6, 1929, to the service of Dr. Herman B. Allyn. Since the age of 10 the patient had been in poor health and complained of generalized joint and extremity pains and frequent sore throats. At the age of 18 she had a long siege of acute rheumatic fever, but her doctor had diagnosed heart disease a few years before this attack. On several occasions she had edema of the ankles.

Physical Examination. The patient was a black female, aged 23 years, poorly developed, poorly nourished and dyspneic. The tonsils were hypertrophied and diseased. The submaxillary glands were enlarged. There was a marked, diffuse precordial pulsation. The apex beat was in the seventh interspace at the anterior axillary line and precordial dullness extended from beyond the right border of the sterum to the axilla. A rough presystolic and a blowing systolic murmur was heard over the entire precordium and was transmitted to the back. The second pulmonic sound was louder than that of the second aortic. The blood pressure was 110 systolic and 75 diastolic. The liver was enlarged to 4 inches below the costal margin and the spleen was easily palpable.

FIG. 1.—Case 1. The vertebræ are shortened in their vertical dimensions and somewhat widened in diameter. They have a soft appearance, there being considerable decalcification. The trabeculæ are rather prominent and sharp and the cancellous spaces are large.

FIG. 2.—Case 1. Left foot. There is considerable osteoporosis. The trabeculæ are sharp and have a pencilled appearance. There are a number of dense lines of bone condensation extending across the medullary cavity. These are particularly prominent in the lower end of the tibia. The cancellous spaces are rather large.

Laboratory Observations. The red blood cells varied from 1,950,000 to 2,700,000; hemoglobin from 40 to 62 per cent. The color index was + 1. The white blood cells varied from 7600 to 13,700 and the differential count was normal. Anisocytosis, poikilocytosis, polychromatophilia and nucleated red blood cells were present on all examinations. Sickle cells varied from 3 to 20 per cent on the stained films. Hemolysis began at 0.46 per cent and was complete at 0.22 per cent salt solution. The blood sugar was 76 mg. and the blood urea nitrogen was 12 mg. per 100 cc. of blood. The icterus index was 12 and the Van den Bergh reaction was delayed. The urine showed a trace of albumin and the specific gravity varied from 1009 to 1012. The electrocardiogram revealed flattened *T* waves in Lead I and inverted *T* waves in Lead II. The *Q–R–S* complexes in Lead I were notched. The roentgenogram of the chest showed considerable pulmonary congestion of both lung bases. There was general cardiac hypertrophy; the heart apex being in the left axilla, and the left auricle much enlarged. The contour of the heart suggested a double mitral lesion with a probable pericarditis. The vertebræ and ribs as shown on a film taken primarily for cardiac study showed no unusual bony lesions.

Course. The patient died 5 months after admission to the hospital. During this time she had frequent episodes of severe lower and upper abdominal pain which were relieved with difficulty only after repeated administrations of morphin.

Case 3.—A colored female child, aged 4 years, was first admitted to the pediatric service of the Philadelphia General Hospital on September 12, 1929. She was a normal baby at birth weighing 7 pounds, 6 ounces. At the age of 4 months she developed rickets and since 2 years of age she had been suffering from anemia, attacks of fever, anorexia, vomiting, pain in the abdomen, back, head and legs. At first these attacks occurred about 1 month apart, but recently they had occurred more frequently. The attacks had often been ushered in by convulsions and a comatose state, suggestive of epilepsy. In the past 2 years she had had a tonsillectomy and several blood transfusions.

Physical Examination. The patient was an anemic, undernourished black girl, aged 4 years, very restless, tossing about, with her legs drawn up. The temperature was 103° F., and the pulse was 120 per minute. Her head was large, flat, and square. The tonsils had been removed. The chest revealed a rachitic rosary. The heart was enlarged to the left and the blood pressure was 130 systolic and 100 diastolic. The spleen was enlarged 4 inches below the costal margin; the liver was not palpable. A small umbilical hernia was present. The cervical and inguinal glands were hypertrophied.

Laboratory Observations. The red blood cells varied from 1,500,000 to 3,800,000; hemoglobin from 40 to 60 per cent. The color index was usually above 1. The white blood cells varied from 4000 to 39,000; of which 40 to 60 per cent were polymorphonuclear leukocytes. Anisocytosis, poikilocytosis, and polychromatophilia were routinely present. Nucleated red blood cells were usually present in varying numbers. Reticulocytes were found ranging from 2 to 10 per cent. Sickle cells varied from a few to very many on the stained films. Clotting time was 3½ minutes and bleeding time 1½ minutes. The platelets varied from 160,000 to 520,000. The blood sugar was 111 mg.; blood urea nitrogen, 16 mg.; calcium, 12.7 mg.; and phosphorus, 4.4 mg. per 100 cc. blood. The spinal fluid Wassermann and bood cultures were repeatedly negative. The von Pirquet test was also negative. The urine showed a trace to a heavy cloud of albumin, occasional granular and many hyaline casts, and a low fixed specific gravity varying from 1003 to 1007.

Roentgenologic Examination. The skull Roentgen ray showed evidence of cerebral atrophy due to intracranial pressure and the typical perpendicular striations of the outer cortex characteristic of sickle-cell anemia. The chest plates showed enlarged glands in the righ hilum shadow. The diaphysis of both femori and both tibiæ were widened and the zone of ossification denser than normal, suggestive of healed rickets. Roentgen ray studies of the spine showed nothing unusual.

Course. From September, 1929, to April, 1930, the patient was admitted to the hospital three times. The critical abdominal attacks, accompanied by fever, vomiting, leukocytosis and pains in the head and extremities were always relieved by blood transfusions. The true nature of the disease was however, not appreciated since sickle cells were either absent on the blood films or were not noticed. The final diagnoses were hilum tuberculosis, chronic diffuse nephritis with acute exacerbations and uremic convulsions, brain tumor, rickets, congenital lues with splenomegaly, anemia, and malnutrition.

On the fourth admission in May, 1930, the diagnosis of sickle-cell anemia was made. A splenectomy was performed by Dr. Eliason on July 1, 1930. This was followed by a good operative recovery and a temporary improvement of the patient's symptoms.

Pathologic Report of the Spleen. The spleen weighed 200 gm. and was of elastic consistency. The surface was irregular because of superficial scars and the capsule overlying the scars was thickened and opaque. The cut surface had a glistening deep red appearance, and the follicles could be distinguished only with difficulty. On microscopy the striking appearance was the extreme congestion. The Malpighian follicles were enlarged and some of them displayed endothelial hyperplasia. Although there was some thickening of the capsule there was but little diffuse fibrosis.

Further Course. Two months after the splenectomy the patient returned to the hospital suffering with the same symptoms that she had had for the past 3 years; namely, headache, back and extremity pains, abdominal rigidity and pain, vomiting and fever. These symptoms were again relieved temporarily by blood transfusions. There have since been two more admissions for similar complaints. The removal of the spleen in this patient has apparently failed either to modify the course or character of the disease or to relieve the distressing abdominal attacks.

Comment. These 3 patients illustrate the salient characteristics of sickle-cell anemia, and more particularly its variable abdominal symptomatology. Our third patient was temporarily relieved by blood transfusions which would suggest that the anemia *per se* may be responsible for the critical episodes under consideration. Any discussion, however, of such abdominal attacks must take into consideration that the disease is notable for its remissions and relapses. Under such circumstances there is no justification in rationalizing a treatment on the favorable outcome of a therapeutic procedure. If any conclusions are to be drawn after the practice of a therapeutic test, the results should be reasonably permanent, constant and clearly related to the treatment. This is not true for our patient and it has not been so for other patients as reported in the literature. The term sicklemia has been suggested instead of sickle-cell anemia because a grave anemia is not constantly found in these patients. It is perhaps best reserved for

those cases that show sickling without anemia. While our 3 patients presented a severe anemia at times, still the abdominal attacks did not necessarily coincide with the periods of marked hemoglobin and red cell depression.

In the matter of remissions and relapses sickle-cell anemia resembles primary anemia, although it differs from this disease in many details. Patients suffering from pernicious anemia seldom have abdominal pains. Baily[20] observed 2 cases of acute abdominal crises in the late stages of pernicious anemia. He operated on the first one and found no lesions aside from a distended gall bladder filled with so-called "biliary mud." Explanation is made to the effect that the liver because of a sudden great blood destruction must secrete large amounts of pigment in a concentrated form and this in turn accumulates in the gall bladder. The weakened patient responds strongly to this painful stimulus. Such a condition has not been found in sickle-cell anemia and therefore can hardly explain the frequent abdominal attacks in sickling patients. It must also be a very rare occurrence in pernicious anemia. Taking, then, all of these comments into consideration it would seem that the anemia of sickling patients is not accountable for their abdominal pains.

The disease resembles hemolytic jaundice in some ways. Sickle-cell anemia is like acholuric jaundice in its hereditary nature, jaundice, blood picture, evidence of blood destruction, relapses and remissions; but differs, in that it seems to be confined to the negro race, shows sickle cells, the atrophic, scarred spleen of older patients, the leg scars, the joint pains, abdominal crises and the failure of splenectomy to cure the condition. Although the hemolytic jaundice patient may have abdominal pains during a severe exacerbation, these attacks are not comparable to those we have observed in sickle-cell anemia. The abdominal pains occurring in the latter disease impress one as being the same sort of pain which is experienced in the extremities and these are absent in the presence of hemolytic jaundice. It must seem apparent to those who have given thought to the matter that the hemolytic features of sickle-cell anemia are not accountable for the critical abdominal attacks.

The pains under consideration may or may not occur in patients with a variable or a constant number of sickle cells. Hahn[11] believes there is a correlation between the severity of sickle-cell anemia and the number of sickle cells in the circulating blood. He further found that symptomless individuals with the sickle-cell trait have few or no sickle cells in the circulating blood. In our first patient, however, studies made of quickly dried smears showed no appreciable variation in the number of sickled cells both in and out of abdominal attacks. It is difficult to estimate the amount of sickling present inasmuch as wet preparations show an increasing number of deformed cells, up to 100 per cent, as time elapses after blood

withdrawal.[23] There is some question as to whether the bizarre forms which are found after a wet preparation stands for a time are identical with those found in blood immediately after the blood has been taken. We have a feeling that examination of a dried smear is the best method of studying sickling quantitatively. On the other hand one is less likely to overlook the presence of sickle cells in doubtful patients by the examination of wet preparations at varying intervals after the blood has been withdrawn. All negro patients should receive the benefit of study in the latter way especially so when they present abdominal symptoms and operation is contemplated.

Hahn[10,11] has shown that the saturation of the blood with CO_2 will produce sickling and that the sickle cells will return to the round form if the blood is then saturated with oxygen. He therefore suggests that anoxemia may be a factor in the production of the sickle-cell distortion in living subjects. With this in mind, our first patient was placed in an oxygen tent during an attack. This procedure did not seem to influence the intensity of his pain or the degree of sickling.

Sydenstricker[23] found that reduction of the blood pH *in vitro* to 7.3 or 7.25 causes immediate sickling. During a symptom-free period in our first patient we tried to produce an attack by the administration of massive doses of ammonium chlorid as well as by feeding a ketogenic diet. As a part of the experiment we also gave the same patient at other times large doses of sodium bicarbonate. These therapeutic trials produced no appreciable change in the patient's condition and were unaccompanied by any change in the degree of sickle-cell formation. While many things seem to influence the amount of sickle cells observed *in vitro*, nothing has been suggested that changes the picture *in vivo*. The administration to our first patient of bicarbonate of soda and potassium citrate together with potassium sulphocyanate was followed on two occasions by an immediate cessation of attacks but no difference in the sickle-cell count. Thus far then, it would seem on the strength of our observations that the mere presence of sickle cells in the circulating blood does not account for the painful episodes.

Inasmuch as the abdominal pains simulate gall bladder attacks on occasions, the question arises as to whether this organ may not be the responsible agent for the abdominal picture under discussion. Hamilton[21] described a case of sicklemia complicated by gall stones, but Hein[22] noted gall stones in only 3 of 12 patients. Our first patient yielded normal cholecystographic studies. Normal gall bladders have been observed in "sicklers" at autopsy who have had attacks of severe pain and rigidity in the upper right quadrant of the abdomen, accompanied by jaundice, vomiting, shoulder and back pain, fever and leukocytosis. This suggests the difficulty of making a decision for or against the presence of gall bladder disease. Yates and Mollari[27] reported a patient who died during an abdomi-

nal crisis as the result, they believed of an arterial thrombosis in the liver. There was however insufficient evidence to substantiate this point. This finding has not been previously reported in sickle-cell anemia and could hardly therefore be counted as the usual cause for the pains with which we are concerned. It would seem then, that the evidence tends to exonerate both the liver and gall bladder as being the usual factor in abdominal pain production for these patients. While the liver is uniformly the seat of pathologic lesions at autopsy, this is not true in the large majority of gall bladders examined at such a time.

Sydenstricker[19] suggests that the usual hypochlorhydria present in this disease may account for some of the gastric manifestations. In the population generally, many individuals present hypochlorhydric states of a like degree but certainly do not have pains which are only relieved by morphin as was true of our first 2 patients.

In addition to morphin, atrophin sulphate, adrenalin hydrochlorid and nitroglycerin were tried hypodermically for our first patient. Calcium and distilled water intravenously also were used.

Many drugs were given by mouth, including the salicylates, and a liver diet plus various liver preparations. None of these therapeutics efforts made an appreciable difference in the severity of the pains. On several occasions it was thought that sterile water hypodermics gave relief, but this was not true during many other attacks. During the remission phases this patient asked for no medication. This seemed to controvert a thought entertained by some that he was experiencing some morphin withdrawal effects. During attacks there was no change in the arterial blood pressure. Whether the pains are a manifestation of some bloodvessel phenomenon, some automatic nervous system disturbance, an allergic state, or some unsuspected condition, must remain an open question. If they are due to one of the above conditions then it would seem that we should have produced some effect by our numerous medicinal practices.

The infarctive[19] and hemorrhagic[17] accidents occurring in the spleen may account for some of the pains. Splenectomy has been performed in a number of sickle-cell patients[10,11,16,24,25,26] with a general but not a uniform improvement in the anemic state. No one has observed a favorable influence on the sickling phenomenon after splenectomy. If the splenic accidents are responsible for the abdominal attacks then we must seek further for an explanation of the very similar chest and extremity pains. Painful abdominal attacks will occur even after splenectomy, as is shown in our third patient who had this operation performed in July, 1930. She was admitted 2 months later because of the recurrence of abdominal pain. Such an experience would indicate clearly that the spleen is not to blame for all of the abdominal symptoms under discussion.

Because of the findings on Roentgen ray examination of definite and extensive lesions in the spine of our first patient, it occurred

to us that the paroxysmal crises in sickle-cell anemia may have their primary origin in these bony lesions. The pains resemble, in a measure, those of root origin as they are found in patients with other vertebral diseases. As far as we are able to determine, no one has carefully studied the nervous system of such patients. The bones of the extremities and skull are not tender nor does the pain seem to be seated in the osseous system. It would seem then that the bony changes as observed by the Roentgen ray are not of themselves responsible for the symptoms complained of by these patients. If not of root origin then the abdominal, extremity and chest pains occurring in our patients may be comparable to the crises of syphilis. In any event, if these pains are not, as they seem to be, of visceral or bony origin, they must be of nervous origin.

Our third patient showed no vertebral Roentgen ray changes and the same is probably true for the second patient as reported. It is quite possible, in spite of these negative findings, that the pains with which we are concerned are nevertheless of a neurologic nature. While muscular rigidity such as was exhibited by our patients is usually due to a visceral lesion still it may result from a so-called "intercostal neuralgia." Carnett[28,29] reported 6 cases of extensive abdominal pain, tenderness and rigidity in the absence of an intra-abdominal lesion. In his numerous contributions on the subject of "intracostal neuralgia" he has shown that "nerve irritation in spinal arthritis is due to an inflammatory exudate in the intervertebral foramina or in the epidural space pressing on the spinal nerves or their roots. This early inflammatory exudate may subside in the later stages with disappearance of sensory symptoms or it may undergo organization with prolongation of symptoms. The extent of bone changes by the Roentgen ray is not an index of the severity of the referred sensory symptoms." While the bony lesion of sickle-cell anemia patients is not inflammatory in nature it is quite possible that the sensory phenomena exhibited by our sickling patients may have a production mechanism similar to that offered in explanation for the spondylitic, even in the absence of Roentgen ray evidence of bone disease.

It is quite probable that the critical episodes occurring in sickle-cell anemia will remain unsatisfactorily explained as long as we are ignorant concerning this disease's causation. Graham theorizes that since these subjects are peculiarly liable to tonsillitis, as was true for our patients, the intermittent attacks may be due to a lighting up of an infective focus. This would explain, he believes, why recurrences take place so frequently after exposure to cold. He further recalls that phagocytosis in the blood by endothelial leukocytes is known in acute and chronic sepsis and especially in infections by the streptococcus. The kidney lesions in this disease are like those produced by the streptococcus. To this we might add that the temperature elevation and leukocytic blood count suggest a microörganismal origin for the disease although no positive blood

cultures have thus far been reported. It may then develop that the pains under discussion are nothing more than the so-called toxic pains which occur in the course of many infectious diseases. They are however peculiarly severe in sickle-cell anemia, if they have such an origin.

Summary and Conclusions. 1. Three patient reports of sickle-cell anemia are presented to illustrate the critical abdominal attacks which may occur in this disease.

2. Current explanations of such paroxysmal abdominal pains as found in the literature are discussed.

3. Other explanations not previously suggested are examined.

4. None of these, whether old or new, are thought to explain adequately the abdominal crises under consideration. It is quite possible that a single explanation may not apply for all of the critical abdominal episodes as they occur in sickle-cell anemia. On the basis of marked bony changes in the vertebræ of our first case we have suggested root pains as a cause for the paroxysmal crises of pain and rigidity.

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UNILATERAL OPACITIES IN CHEST FILMS.

By J. J. Singer, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE.

(From the Department of Medicine of Washington University and the Medical and Surgical Chest Service, Barnes Hospital, St. Louis, Mo.)

The differential diagnosis of unilateral opacities in chest films offers considerable difficulty because a similar shadow can be produced by many causes.

Careful analysis of the symptoms, together with physical signs and laboratory methods, often gives one sufficient data upon which to base a diagnosis; but the Roentgen ray interpretation often gives the convincing clue as to the exact condition present.

There are certain conditions in the chest which with our present knowledge can only be recognized by biopsy, and at times only by autopsy. Such methods as proper positioning under the Roentgen ray, bronchography and more frequent bronchoscopies have aided us considerably in clearing up many otherwise puzzling problems.

The physical conditions of the chest which may produce opacities in the Roentgen ray film are as follows: Tumors of the chest wall, fluid in the pleural cavity, tumors of the pleura, atelectasis of the entire lung, pneumonia, tuberculosis, many other massive infections of the lung and marked pleural thickening or fibrosis.

It is the purpose of this paper to demonstrate the ease with which the observer may often solve the problems incident to interpreting unilateral opacities if he makes use of all methods of diagnosis.

Case Reports. Case 1.—*Mediastinal Tumor (Hodgkin's Disease) with Pleural Effusion.* C. C., a woman, aged 24 years, was admitted to the Barnes Hospital, February 20, 1930, with a history that since October, 1929, she had lost strength and had suffered sharp stabbing pain in the right upper chest associated with cough. An afternoon rise in temperature (101° F.) was noted in November, 1929. The pain increased in severity, dyspnea appeared and the patient was admitted to the Missouri Baptist Hospital, January 16, 1930. On February 1, 1930, her face, arms and neck began to swell. Because the presence of fluid was suggested by a Roentgen ray film, an attempt was made anteriorly to withdraw it. A small amount of pus was obtained, probably from a bronchus. Aspiration in the right axillary line yielded serous fluid.

Upon admission to the Barnes Hospital it was noted that the patient had marked swelling of the face, neck and right arm. She was orthopneic and rather pale. Her blood pressure was 108 systolic and 68 diastolic, the same in both arms. Physical findings were all referable to the right chest. On questioning it was found that she also suffered from sternal tenderness and general itching. Her leukocyte count was 18,900, with a relative preponderance of polymorphonuclear cells (90 per cent); there was no eosinophilia. Laboratory findings were negative.

Aspiration of the chest in the right midaxillary line on February 21 yielded

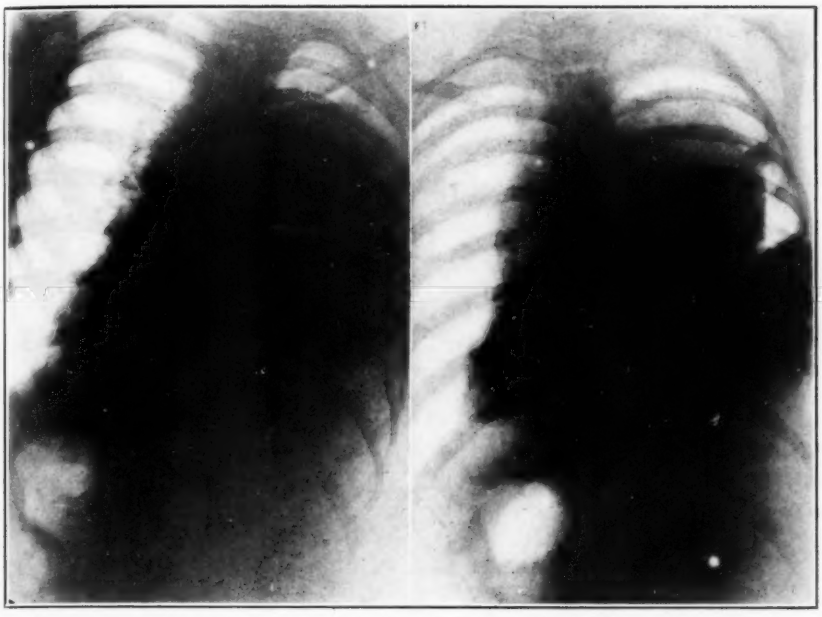


FIG. 1, *a*.—February 24, 1930. Unilateral opacity in the right chest from the first anterior rib which merges with the shadow of the liver. The heart and upper mediastinum are pushed toward the left. There is compensatory air content in theleft lung.

FIG. 1, *b*.—February 24, 1930. Film taken after the aspiration of 400 cc. of clear fluid and the replacement by 100 cc. of air (diagnostic pneumothorax). A dense mass is now visible and a fluid level at the base is noted. The patient was slightly rotated to exaggerate the shadow. Diagnosis: Mediastinal tumor, probably Hodgkin's disease or lymphosarcoma.

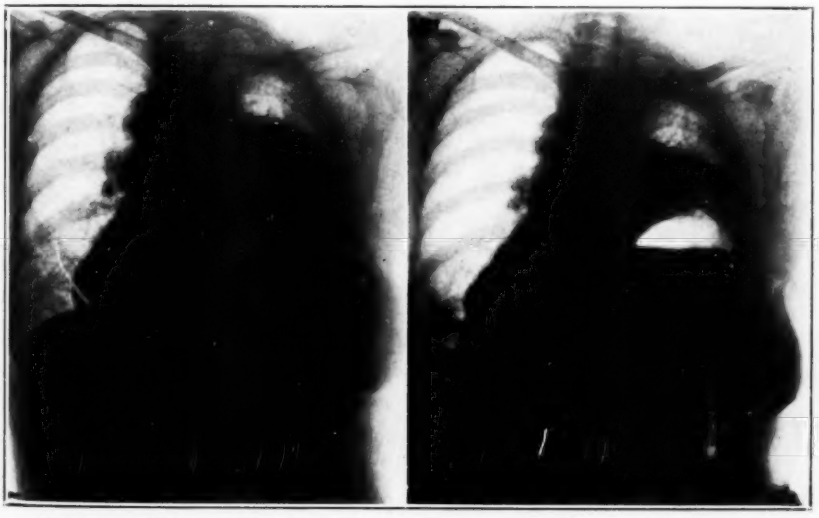


FIG. 2, *a*.—February 23, 1924. The Roentgen ray film shows a unilateral opacity in the right chest from the first rib and merging with the shadow of the liver. (Note similarity of Fig. 1, *a*.)

FIG. 2, *b*.—February 23, 1924. Film taken after the aspiration of 400 cc. of fluid and the replacement of 100 cc. of air. Note the dense mass made by visible the diagnostic pneumothorax. Note the fluid level. It is evident from this study that a distinct tumor is present in the right lung. (This was later proven by operation.)

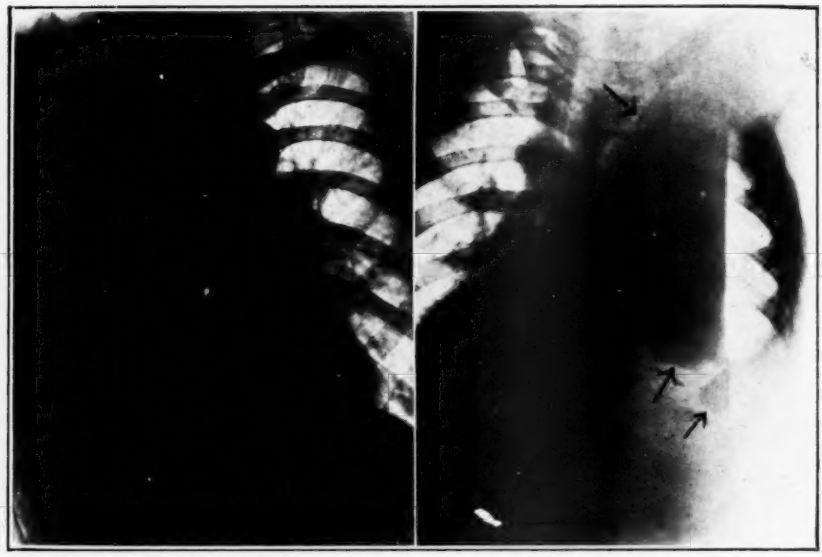


Fig. 3, *a*.—January 28, 1930. Unilateral opacity of the entire right thorax. No lung detail is noted. The left lung is normal. No definite diagnosis could be made, although many possibilities were suggested. A diagnostic puncture was made, pinkish-yellow fluid resembling pus was withdrawn and 100 cc. of air were introduced; a small amount of iodized oil was also introduced into the pleural cavity.

Fig. 3, *b*.—January 31, 1930. Film taken with the patient lying with the right side up. The diagnostic pneumothorax shows the presence of a large encysted collection of fluid and a smaller one below (this is well outlined with lipiodol). At operation a large cyst was noted in the right pleura, but no hooklets (echinococcus) were found. Diagnosis: Echinococcus (?) cyst or amœbic abscess. (Should be viewed horizontally with right side up.)

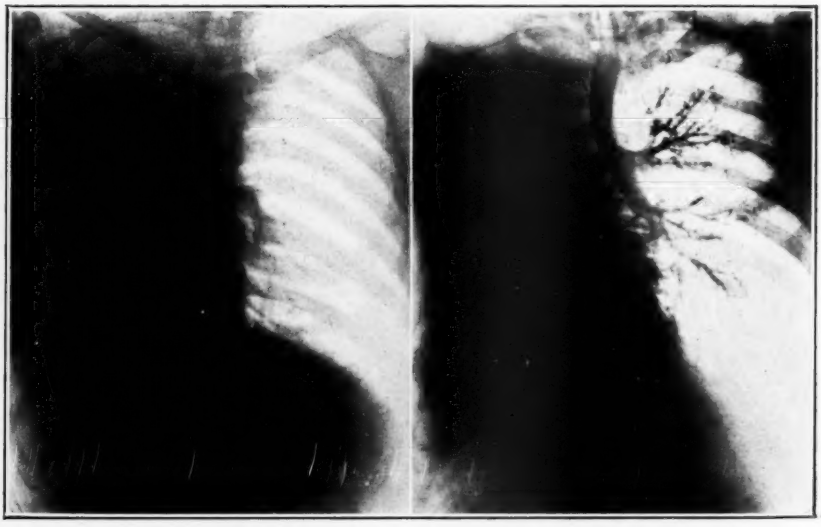
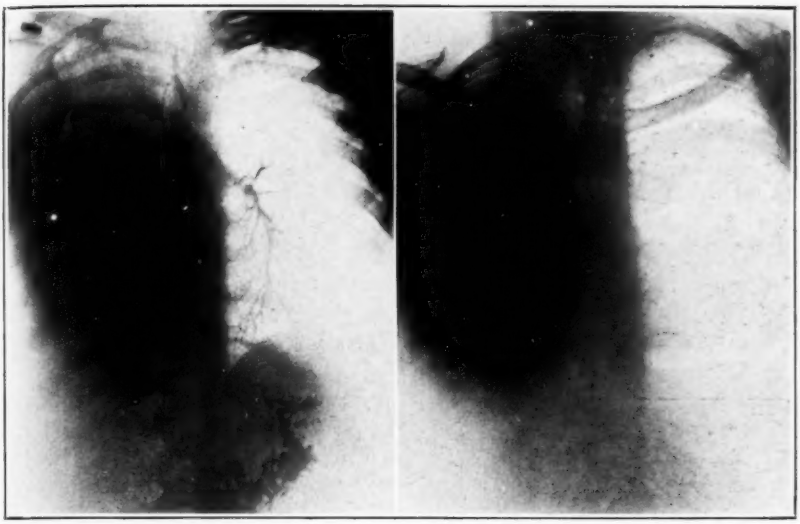


Fig. 4, *a*.—October 30, 1928. Unilateral opacity of the entire left side. Note the deviation of the trachea (left). No cardiac shadow is seen in the right side. The physical signs suggested fluid and aneurysm. Diagnosis: Massive collapse due to obstruction of the main left bronchus.

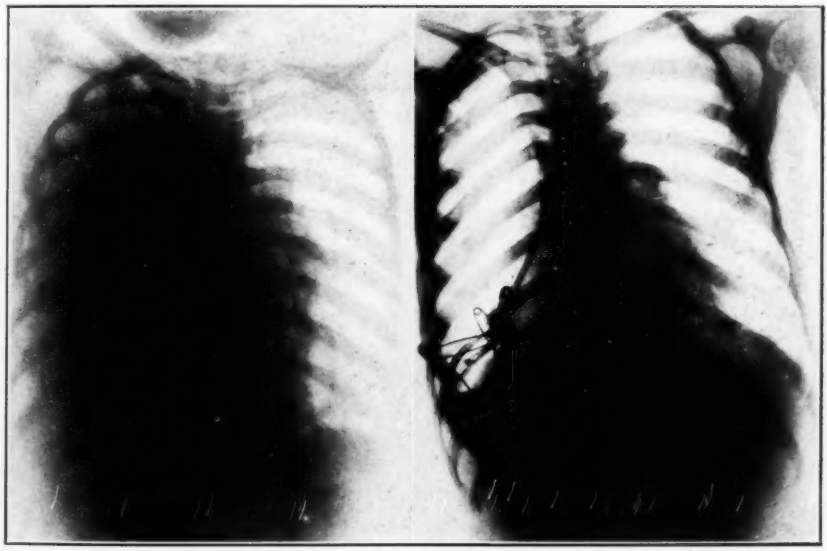
Fig. 4, *b*.—December 10, 1928. Lipiodol shows complete obstruction of the main left bronchus. Note the visibility of the vertebræ as a result of the retraction of the left lung. Autopsy disclosed rupture of aneurysm of the aorta and massive atelectasis of left lung probably from compression of left main bronchus.



a *b*

FIG. 5, *a*.—June 6, 1929. Lipiodol introduced by the aspiration method shows the trachea and the main right bronchus dilated, the upper bronchus blocked, the middle partially and the lower one completely. The left bronchial tree is normal. There is some oil in the stomach. Diagnosis: Pulmonary tuberculosis with fibrosis and partial atelectasis of the right lung.

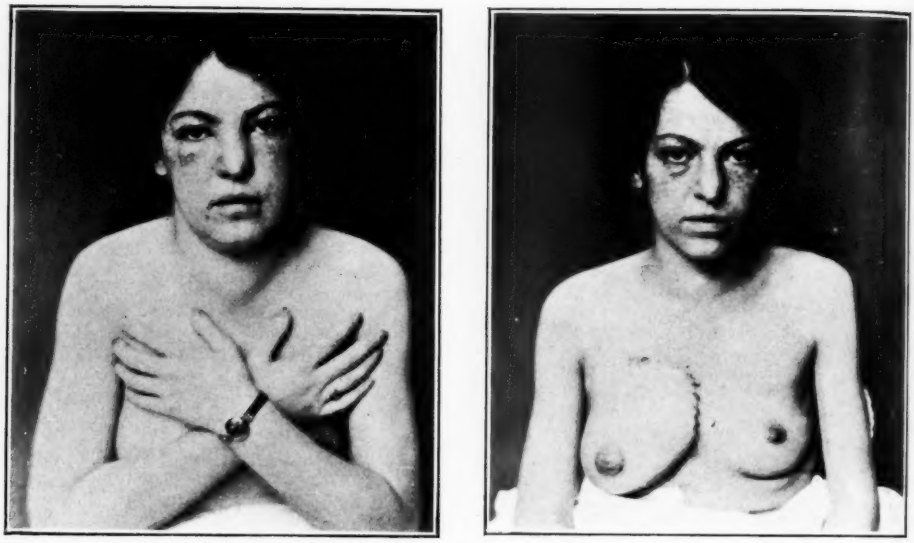
FIG. 5, *b*.—September 9, 1929. Unilateral opacity of the right lung. Note the deviation of the trachea to the right. Below the right clavicle there is a crescentic-like area of rarefaction. The right diaphragm is not visible. The left lung shows compensatory air content. The cardiac shadow is retracted to the right. Impression: Pulmonary tuberculosis with fibrosis of the lung.



a *b*

FIG. 6, *a*.—January 20, 1930. Unilateral opacity of the entire right chest. Heart displaced to the left. No pulmonary markings noted. Signs of fluid. An aspiration showed a large amount of purulent fluid.

FIG. 6, *b*.—February 5, 1930. Film of patient after thoracostomy and drainage. The lung is partially expanded. Surgical pneumothorax (Dakin tubes in place). The heart has returned to its proper position. Diagnosis: Empyema, right pleura.



a *b*

FIG. 7, *a*.—March 6, 1930. Photograph taken before the operation, showing edema of face and arms.

FIG. 7, *b*.—March 21, 1930. Photograph showing the condition after the decompression operation. Note the diminution of the swelling, also the scar.

1200 cc. of thin straw-colored fluid. The laboratory findings were negative. There were repeated aspirations. A diagnostic pneumothorax was done.

Roentgen ray examination: (Fig. 1, *a*.) February 24, 1930: Unilateral opacity in the right chest from the first anterior rib which merges with the shadow of the liver. The heart and upper mediastinum are pushed toward the left. There is compensatory air content in the left lung. Fig. 1, *b*, film taken, February 24, 1930, after the aspiration of 400 cc. of clear fluid and the replacement by 100 cc. of air (diagnostic pneumothorax). A dense mass is now visible and a fluid level at the base is noted. The patient was slightly rotated to exaggerate the shadow. Diagnosis: Mediastinal tumor, probably Hodgkin's disease or lymphosarcoma.

The diagnostic pneumothorax disclosed a dense mass (Fig. 1, *b*), apparently mediastinal, with collapsed right lung and free fluid in the pleural cavity. After the aspiration of 300 to 500 cc. of fluid the edema of the face, neck and arm diminished. It was, therefore, presumed that there had been definite compression of the superior vena cava.

After the analysis of the signs, symptoms and Roentgen-ray studies the following diagnoses were considered: (1) Mediastinal tumor, Hodgkin's disease; (2) serofibrinous pleurisy, tuberculosis; (3) atelectasis of the lung due to fibrosis; (4) endothelial tumor.

As the shadow in the right chest was homogeneous, the question arose whether the lung or the pleura was involved. Only a small part of the injected iodized oil entered the right bronchial tree because in all probability there was a pathologic compression of the main bronchus. Confirming this probability was the presence of fluid in the pleura. The blood picture was somewhat suggestive of Hodgkin's disease. The aspirated fluid was centrifuged, but no tumor cells were found. The sputum was consistently negative for tubercle bacilli. No glands were palpable for biopsy.

Deep Roentgen ray therapy was started on February 24 and was continued at intervals of several weeks. As the mass did not disappear after several Roentgen ray exposures and the dyspnea and cyanosis became alarming, it was decided to do a decompression of the anterior right chest. Dr. Evarts Graham removed portions of the second and third right costal cartilages. When the mediastinum was exposed a large firm, slightly gray, nodular mass was found firmly attached to structures within the chest wall and presenting all the characteristics of a malignant tumor. The diagnosis of a small portion removed for microscopic examination was Hodgkin's disease. Following the operation the edema of face, neck and hands disappeared and the patient steadily improved. The question arose as to whether the Roentgen ray treatment or the decompression produced this change.

Following the operation, the wound healed promptly and the patient improved remarkably. She was discharged from the hospital, March 25, 1930, and has returned from time to time for observation and Roentgen ray treatment. Improvement was marked for 7 months, at which time metastasis occurred in the right chest wall involving the 3 lower ribs.

In the light of all the clinical data, a diagnosis of tumor of the mediastinum (Hodgkin's disease) was made. A study of the Roentgen ray films shows how much information may be obtained by a diagnostic pneumothorax. (Fig. 7, *a* and *b*.)

CASE 2.—*Carcinoma of the Left Lung With Metastasis to the Ilium.* C. S., a woman, aged 65 years, was admitted to the Barnes Hospital, February 23, 1924, with a chief complaint of pleurisy on the right side.

In November, 1923, her right ankle was swollen for 1 week. She also noted at that time a dull pain at the right waistline which lasted 2 weeks. She suddenly became dyspneic and went to bed. There was no fever, cough nor pain in the chest, but the pain at the waistline persisted. On

December 9, 1923, the patient was taken to a hospital after an aspiration showed the presence of serous fluid. Several thoracenteses were performed; each time 500 to 1000 cc. of similar fluid were obtained. All the patient's Roentgen ray films taken in December before leaving the hospital showed a right unilateral opacity of almost the whole right chest. Three weeks before admission to Barnes Hospital a "hacking" cough had developed, but the dyspnea was better. A week later her right leg was painful when walking. She had a poor appetite and lost 20 pounds in weight.

The physican signs at the time of admission showed flatness and absent breath sounds in the right chest with compensatory sounds in the left lung. The heart was not displaced.

Roentgen ray examination: (Fig. 2, *a*.) February 23, 1924: The Roentgen ray film showed a unilateral opacity in the right chest from the first rib and merging with the shadow of the liver. (Note similarity of Fig. 1, *a*.) Fig. 2, *b*, a film taken, February 23, 1924, after the aspiration of 400 cc. of fluid and the replacement of 100 cc. of air. The dense mass made visible by the diagnostic pneumothorax and a fluid level were noted. It is evident from this study that a distinct tumor was present in the right lung. (This was later proven by operation.)

In order to establish the factors producing the dense shadow a thoracentesis was done, followed by a diagnostic pneumothorax. A fluoroscopic examination was then made. By viewing the patient in the lateral, upright and inverted positions, the injected air made it possible to outline a tumor mass in the midportion of the right lung.

A clinical diagnosis of questionable malignancy of the lung was made on the following data: Age, duration of disease, absence of fever, general weakness and signs of metastasis in the ilium.

Discussion. The probable diagnosis before the aspiration and the peumothorax were done was similar to Case 1, that is, a massive tumor of the chest with fluid in the pleura. After the air was introduced the probability of a lung abscess or lung tumor was considered. The lesions in the liver and right ilium suggested metastases. An operation disclosed a mass in the right lung, a section of which showed this to be a bronchogenic carcinoma.

This case also shows how a diagnostic pneumothorax may help in the interpretation of the Roentgen ray film.

CASE 3.—*Cysts of the Right Pleura* (*Echinococcus or Amœbic?*). J. W., a man, aged 41 years, was admitted to the Barnes Hospital, January 28, 1930, with the following complaints: Pain in the right chest, productive cough, shortness of breath, weakness, loss of weight and nightsweats.

The significant points of his past history were as follows: At about 12 years of age the patient worked in a slaughter house after school for a period of 2 years. At that time he had repeated attacks of diarrhea and occasional attacks of sore throat. He had three attacks of "quinsy" and had occasional attacks of pain in the right shoulder, radiating anteriorly around the chest and localizing in the right upper quadrant. Vomiting without nausea had occurred at intervals of 1 to 2 weeks for many years. In August, 1928, he was jaundiced for a period of several weeks.

His present illness began in January, 1929, with severe attacks of pain in the right shoulder, radiating to the right upper quadrant associated with jaundice. He was sent to a hospital, where a tentative diagnosis of carcinoma of the liver, cholecystitis and cholelithiasis was made. At operation the gall bladder and appendix were removed. No stones were found in the gall bladder, however, and this organ did not seem definitely diseased. For some time following the operation jaundice persisted and the patient still complained of pain in the right upper quadrant. Convalescence was otherwise uneventful and the patient returned to his home.

In June, 1929, his symptoms—cough, productive of white sputum, night-sweats and weakness—became more marked, and he developed a sudden sharp pain in the lower chest. He reëntered the hospital, where evidence of fluid in the right pleural cavity was found. A thoracentesis was performed and about "1 gallon of pink-colored fluid" was obtained. Several other thoracenteses were performed; large amounts of fluid were withdrawn. The patient stated that this fluid was of a dark reddish-brown color After 2 weeks in the hospital he was discharged. During the following months his symptoms were slightly improved.

In November, 1929, the patient had another attack of "quinsy" and in the same month had a tonsillectomy. About Christmas time all his symptoms became aggravated. Two weeks before admission to the Barnes Hospital his family physician attempted a thoracentesis, but no fluid was obtained; a second attempt was made with success. At the time of admission to Barnes Hospital the positive physical findings were flatness on percussion over the entire right chest, diminished breath sounds and diminished and absent vocal fremitus over the same area. The heart was moderately displaced to the left. There was harsh compensatory breathing over the entire left chest. No râles were heard. The abdomen showed a right rectus scar. There was tenderness along the right costal margin and the liver was palpable 2 finger breadths below the costal margin on the right.

Roentgen ray examination: (Fig. 3, *a*.) January 28, 1930: Unilateral opacity of the entire right thorax. No lung detail is noted. The left lung is normal. No definite diagnosis could be made, although many possibilities were suggested. A diagnostic puncture was made, pinkish-yellow fluid resembling pus was withdrawn and 100 cc. of air were introduced; a small amount of iodized oil was also introduced into the pleural cavity. Fig. 3, *b*, film taken, on January 31, 1930, with the patient lying with the right side up. The diagnostic pneumothorax shows the presence of a large encysted collection of fluid and a smaller one below (this is well outlined with lipiodol). At operation a large cyst was noted in the right pleura, but no hooklets (echinococcus) were found. Diagnosis: Echinococcus (?) cyst or amœbic abscess.

Discussion. The history and physical signs suggested an empyema following the gall bladder operation. This condition may or may not have been associated with a pulmonary abscess or subphrenic abscess, although there was no sputum for several weeks.

The history of long-standing diarrhea with bloody discharges, and the fact that amœbæ were found in the stool, suggested an amœbic abscess of the liver with secondary involvement of the pleura. The complement fixation test for echinococcus infection was 2+ on two occasions. Because of the similarity of the signs and symptoms of echinococcus and amœbic infections we were in doubt of the diagnosis. A Casoni test was negative. Treatment with emetin was instituted.

Case 4.—*Aneurysm Compressing the Left Bronchus* (*Massive Atelectasis*). J. S., a man, aged forty-eight years, was admitted to the Barnes Hospital on December 4, 1928, complaining of pain over the heart, shortness of breath, loss of 20 pounds of weight and a cough. The patient gave a history of having always been well until about June, 1928, when he noticed he was short of breath; however, he had previously noted a "neuritis" across the upper back and shoulders which was aggravated by exertion. Two months before entering the hospital he had some pain over the region of the heart, which gradually became worse. Just 10 days before admission a cough which seemed associated with the pain over the heart was noted and the sputum was frequently blood streaked.

Physical findings upon admission showed a tracheal tug, and the chest examination showed the left side to be smaller and the movements less

than on the right; physical signs showed evidence of compression of the bronchi of the left lung and fluoroscopy and Roentgen ray films showed a high immobile left diaphragm with density throughout the left lung field. The heart examination showed expansile pulsation in the first intercostal space left, 3.5 cm. to the left of the sternum. The heart measured 14 cm. to the left. The sounds were loud; there was a systolic murmur over the precordium and a diastolic murmur heard best along the left border of the sternum. The blood pressure was 126 systolic and 45 diastolic in the left arm and 126 systolic and 54 diastolic in the right arm.

The sputum was negative for tubercle bacilli, occasionally it was blood tinged. The urine was negative. The Wassermann and Kahn tests were 4+. The patient's blood count showed 5,200,000 red blood cells, 90 per cent hemoglobin and 11,300 white blood cells.

Bronchography showed lipiodol blocked at the main left branchus. A diagnostic pneumothorax showed a pulsating shadow in the upper mediastinum, left. The left lung was collapsed and a small amount of fluid was seen at the base. On December 17, 1928, 350 cc. of pink opalescent fluid were aspirated from the left pleural cavity; 175 cc. of air were introduced, and it was seen that the mediastinum was still displaced. A few days later 150 cc. of blood-tinged fluid were aspirated from the left pleural cavity.

On December 26, 1928, paradoxical movement of the left diaphragm was noted. On this same day the patient had been coughing up blood, but was in good condition. During the night he was awakened from sleep by a massive hemorrhage in the mouth; he then lost consciousness in a few moments and died. An autopsy was performed disclosing a ruptured aneurysm of the aorta; the aneurysm had obstructed the left bronchus and had given rise to a massive atelectasis of the left lung.

Roentgen ray examination: (Fig. 4, *a*.) October 30, 1928: Unilateral opacity of the entire left side. Note the deviation of the trachea (left). No cardiac shadow is seen in the right side. The physical signs suggested fluid and aneurysm. Diagnosis: Massive collapse due to obstruction of left main bronchus. (Fig. 4, *b*.) December 10, 1928: Lipiodol shows complete obstruction of the main left bronchus. Note the visibility of the vertebræ as a result of the retraction of the left lung. Autopsy disclosed rupture of aneurysm of the aorta and massive atelectasis of left lung, probably from compression of left main bronchus.

Discussion. The history and physical findings of this case are quite suggestive of aneurysm. The various examinations suggested syphilis with aortic aneurysm but the unilateral opacity confused the picture. We thought that there was a tumor compressing the left main bronchus. Following the diagnostic pneumothorax, one could readily see from the Roentgen ray film that the aortic shadow was not much enlarged. Fluid from an atelectatic lung could be due to an intrabronchial tumor. There were no glands for biopsy. Bronchoscopy was considered as a diagnostic measure, but the danger of rupture of an aneurysm, if present, delayed the procedure. Postmortem showed an aneurysm of the arch of the aorta which had ruptured into the left main bronchus. The aneurysm itself was quite small, compressing the lumen of the bronchus almost to obliteration.

Case 5.—*Tuberculosis of the Right Lung* (*Atelectasis*). T. W., a white man, aged 32 years, had symptoms of tuberculosis in the right lung with positive sputum. He had pneumothorax treatment elsewhere which was complicated later by massive pleural effusion. Repeated aspirations were done. On admission the physical signs were dullness throughout and bronchial breathing throughout the right chest, but no râles. His general condition was excellent.

Roentgen ray examination: (Fig. 5, *a*.) June 6, 1929: Lipiodol intro-

duced by the aspiration method shows the trachea and the main right bronchus dilated, the upper bronchus blocked, the middle partially and the lower one blocked completely. The left bronchial tree is normal. There is some oil in the stomach. Diagnosis: Pulmonary tuberculosis with fibrosis and partial atelectasis of the right lung. (Fig. 5, *b*.) September 6, 1929: Unilateral opacity of the right lung. Note the deviation of the trachea to the right. Below the right clavicle there is a crescentic-like area of rarefaction. The right diaphragm is not visible. The left lung shows compensatory air content. The cardiac shadow is retracted to the right. Impression: Pulmonary tuberculosis with fibrosis of the lung.

Discussion. As the Roentgen ray film shows a unilateral density the state of the bronchial tree is not apparent. By the introduction of the iodized oil its true condition was demonstrated. A diagnostic chest puncture was made to rule out the presence of fluid.

This case demonstrates the value of iodized oil in analyzing the condition of the bronchial tree.

NOTE.—The iodized oil was introduced by the aspiration method without the use of a local anesthetic. No reaction followed.

CASE 6.—*Empyema, Right Pleural Cavity.* L. F., a white boy, aged 15 years, was admitted to the Barnes Hospital, January 20, 1930, with a diagnosis of pneumonia. On December 9, 1929, he had an attack of pneumonia of the left lung which lasted 9 days. He seemed to be improving until 2 weeks before admission, when apparently pneumonia developed on the other side of his chest. At admission there were signs of consolidation and of fluid over the entire right chest, with rapid pulse (145), rapid respiration, cough, some expectoration of frothy fluid and cyanosis.

Roentgen ray examination: (Fig. 6, *a*.) January 20, 1930: Unilateral opacity of the entire right chest. Heart displaced to the left. No pulmonary markings noted. Signs of fluid. An aspiration showed a large amount of purulent fluid. (Fig. 6, *b*.) February 5, 1930: Film of patient after thoracostomy and drainage. The lung is partially expanded. Surgical pneumothorax (Dakin tubes in place). The heart has returned to its proper position. Diagnosis: Empyema, right pleura.

Aspirations of pus were made on January 21 and 22 followed by some relief. Because of the displaced heart and mediastinal contents, rapid pulse, fever, dyspnea and cyanosis, open drainage was delayed until January 24, when a thoracostomy with rib resection was performed by Dr. Graham. The cavity diminished in size rapidly and the patient was discharged on March 4, 1930.

Discussion. The history and physical signs and the Roentgen ray examination suggested fluid throughout the right chest, even before diagnostic puncture. The heart was displaced beyond the left mammary line; the trachea was not displaced and the diaphragm was not high. These findings show no evidence of massive collapse. Against pneumonia was the evidence of displaced mediastinum and the clinical history. The fluid aspirated proved to be thick pus. It was only after the aspiration of the pus that the true character of the disease was recognized.

Summary. The correct diagnosis of those conditions of the chest which produce unilateral opacities in the Roentgen ray films cannot be made from the Roentgen ray film alone. Six different cases have been presented in support of this view. The correlation of history and physical signs with the diagnostic procedures of bronchography and diagnostic pneumothorax are necessary.

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SUPERFICIAL THROMBOPHLEBITIS: A NEW CAUSE OF CHEST PAIN.

By Worth B. Daniels, M.D.,

CLINICAL PROFESSOR OF MEDICINE, GEORGETOWN UNIVERSITY, WASHINGTON, D. C.

(From the Medical Department of Georgetown University School of Medicine.)

During the past 3 years I have encountered 5 instances of pain in the chest due to an unusual cause. In an extensive review of the literature no mention is to be found of this entity as an etiologic agent of thoracic pain. It seems, therefore, worth while to report these cases as an aid in differential diagnosis.

Case Reports. Case 1.—A colored male, aged 45 years, was seen on the wards of Garfield Memorial Hospital during the summer of 1927. This was a week following the onset of pain in the right chest, which was accentuated by deep breathing. He complained, too, of tenderness over the right lateral chest. On examination a tender sinuous cord, roughly 0.4 cm. in breadth, could be felt in the subcutaneous tissue. This cord extended from the right epigastrium upward and laterally to a point just outside the nipple where it was no longer palpable. It could be rolled under the fingers and was distinctly tender on palpation. The examination of the chest was otherwise normal. The further course is unknown.

Case 2.—P. S. L., a colored female houseworker, aged 47 years, was seen in the outpatient department of Garfield Memorial Hospital on July 11, 1928. She complained of pain in the left chest of 3 weeks' duration. The pain was accentuated by deep breathing and by pressure. There had been no cough or other symptoms. No history of injury. One week previously a member of the staff had made a diagnosis of pleurisy and strapped the chest with adhesive. This gave no relief. On examination, after the strapping had been removed, a rounded cordlike structure could be felt running from the left epigastrium upward toward the axilla and passing just lateral to the left breast. The cord could be rolled under the fingers and was distinctly tender. The treatment consisted only of cold applications for relief of pain. The patient was again seen 6 months later

when there was no remaining abnormality. There had been no recurrence of pain.

CASE 3.—T. C. E., a white male Government employee, aged 50 years, was seen in my office on July 28, 1928, complaining of pain in the right chest just lateral to the nipple line. There was no relationship to deep breathing but the pain seemed to be distinctly increased on raising the right arm. Seven weeks before the present trouble began, a partial resection of the colon had been done because of acute diverticulitis. This was done through a left rectus incision but an enterostomy tube was left in the right lower quadrant for a few days postoperative. On examination of the chest there was localized tenderness in a line extending from the fourth interspace just lateral to the nipple downward and medially as far as the seventh interspace. A distinct cordlike structure about the size of a goose quill could be felt in the subcutaneous tissue. This cord could be rolled under the fingers and was quite tender. The temperature was normal. The postoperative course had been uneventful and there was no evidence of wound or skin infection. The pain and tenderness disappeared quickly without treatment. At present the cord cannot be felt and there are no residual symptoms.

CASE 4.—H. E. G., a white male office worker, aged 26 years, came into my office on February 6, 1929, complaining of pain in the right chest. He had had a healthy life and his past history threw no light on the present illness. Two weeks previously he noticed pain in the right chest near the costal margin in the region of the nipple line when he raised his arm. There also was tenderness on pressure in this region. A few days later the pain shifted upward to the sixth interspace, just lateral to the nipple line, and became more acute. There was an accentuation of the pain on deep breathing, coughing or sneezing. He applied local heat and massaged the area with counterirritants, but the pain persisted. Examination revealed a well-nourished, healthy looking young man with a temperature of 99.6° F. On the anterolateral portion of the right chest extending from the fifth interspace just lateral to the nipple line downward and medially to the epigastrium, a tender, rounded cord was palpated. This cord was about 0.3 cm. in breadth and could be rolled under the fingers. There was no tenderness except on direct pressure on the cord. When the arm was raised there was puckering of the subcutaneous tissue throughout the length of the structure described. It was not otherwise visible. No treatment was instituted except local cold applications for relief of pain. On February 14, 8 days later, the patient was seen again. The pain and tenderness in the original cord had disappeared, but it was firmer and more easily felt. Its course was longer, extending from 1.25 cm. above the costal margin to the level of the nipple. Its direction was toward the axilla. A similar tender sinuous structure was now noted running transversely from the original cord as far as the anterior axillary line at the level of the nipple. Physical examination otherwise revealed no abnormality. The urine was entirely normal, the leukocyte count was 9650; polymorphonuclear neutrophils, 75 per cent; large mononuclears, 2 per cent; transitionals, 2 per cent; lymphocytes, 21 per cent.

Two days later there was again a slight return of tenderness in the first vein involved, but less tenderness in the tributary. Ten days later all tenderness had disappeared from both veins and only the original cord could be palpated over a very short course. On June 28, 1929, 4 months after the first disturbance, the patient returned, complaining of exactly the same trouble but in the opposite chest. There was pain in the left chest on deep inspiration, on raising the left arm and distinct tenderness along the course of the vein. The vein involved was sinuous and markedly tender. It could be rolled under the fingers and extended about 12.5 cm. in length. Its course was vertical about 4 cm. lateral to the left nipple.

The temperature was 99.8° F. The leukocyte count was not unusual. Examination again was otherwise normal.

When seen 5 months later there was no palpable or visible abnormality on either side of the chest. The patient has remained well.

CASE 5.—Miss A. L., a white, unmarried Government employee, aged 46 years, came into the office on December 20, 1929. She complained of a sense of tightness in the lower left chest and upper epigastrium just lateral to the midline. This had developed 3 or 4 months previously and was associated with rather acute discomfort in the chest on deep inspiration. Soon after the onset the patient discovered a tender cord beneath the skin of the lower chest and upper epigastrium. Her previous history revealed nothing which threw light on the present illness. She had been thoroughly studied by me about a year before, because in a routine ophthalmologic examination an early retinal arteriosclerosis was noted. At that time, aside from the general atherosclerosis, albuminuria and cylindruria, no abnormalities were found. There was no enlargement of the heart and the kidney function was normal. The blood pressure was 120 systolic and 80 diastolic. On examination a distinctly tender subcutaneous cordlike structure about 0.3 cm. in diameter could be felt and rolled under the fingers. The cord extended from just above the umbilicus curving upward and outward almost to the left nipple. No treatment was advised. One month later the patient notified me that the sinuous structure had gradually extended downward to the umbilicus and then slowly disappeared. She is at present entirely well.

Comment. The obvious diagnosis in all these cases is a thrombophlebitis involving a superficial vein, which extends from the axilla downward and slightly medially toward the region of the umbilicus. It is most probably the thoraco-epigastric branch of the axillary vein. It is interesting that in each instance the pain is accentuated by deep breathing due undoubtedly to the stretching of the involved vein over the flaring costal border. In Case 2 the pain was so like that of fibrinous pleurisy that a member of the dispensary staff had previously strapped the chest. In no case was the cordlike vein visible and its presence was only recognized by gently passing the fingers over the skin of the chest. It is probable, therefore, that added attention to palpation in instances of chest pain will reveal more cases of superficial thrombophlebitis.

No etiology was ascertained for the disturbance reported except in Case 3. Here the thrombophlebitis was probably secondary to a low-grade infection of the abdominal incision. In none of the cases was there a history of syphilis or trauma. There was nothing present which could cause local stasis and there was no infection of the adjacent skin or subcutaneous tissue.

In 1922 Fiessinger and Mathieu[1] reported 3 cases of thrombophlebitis of the thoraco-abdominal wall following grippe-like infections. Two of their cases involved largely the abdominal portion of this same vein, the other was practically identical with the cases under discussion. Pain was not a feature in their report, though 1 patient did complain of slight epigastric discomfort. It is easily conceivable that painful involvement of the abdominal segment of

the vein might give trouble in the differential diagnosis of upper abdominal pain.

Summary. 1. Six instances of thrombophlebitis of a superficial chest vein are reported.

2. Chest pain was the predominant symptom.

3. Recovery without complication was the invariable outcome.

NOTE.—Since acceptance of this paper, a case report by Dr. George A. Williams, of Atlanta, describes in the *Journal of the American Medical Association*, 1 case with identical findings. This case was associated with dyspnea.

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THE SIGNIFICANCE OF THE COLLOIDAL GOLD REACTION AS A DIAGNOSTIC AND PROGNOSTIC AID IN NEUROSYPHILIS.*

BY FREDERICK G. NOVY, JR., M.S., M.D.,

INSTRUCTOR IN DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR, MICH.

FROM the time Lange, in 1912, published his results on the colloidal gold reaction there has been a great deal written, particularly as to its value in differentiating the various forms of central nervous system syphilis. As is well known, considerable difference of opinion exists as to its specificity, especially in types other than general paresis. Information on the effect of antisyphilitic therapy on this test has for the most part been scanty, references being found either in a general discussion of the reaction or in the results with some type of treatment. Here again, the conclusions regarding the value of the changes found have been varied.

For these reasons, a study has been undertaken in this clinic to determine the correlation between the clinical diagnoses and the colloidal gold reactions in cases of untreated neurosyphilis and the type of change found in cases undergoing treatment. Most of the material for this study came from cases admitted to the department of dermatology and syphilology in the last 5 years. A few cases, however, were seen in the department of neurology. The clinical diagnosis was made only after the patients had been thoroughly studied.

The colloidal gold reaction was performed in the serological

* Studies and contributions of the Department of Dermatology and Syphilology of the University of Michigan Medical School, service of Dr. Udo J. Wile.

laboratory of the hospital. All colloidal gold solutions employed conformed to the following requirements: (1) Transparency of a brilliant salmon color with no trace of blue; (2) 5 cc. decolorized by 1.7 cc. of a 1 per cent sodium chlorid solution; (3) neutrality to alizarin red; (4) typical paretic curve with known paretic spinal fluid; (5) no change in color beyond a faint "red-blue" with a known normal spinal fluid. As a reducing agent in the preparation of the colloidal gold solution, formaldehyde was used up to September, 1929, and glucose since then.

The tests were carried out in the usual manner. The spinal fluid dilutions in 0.4 per cent sodium chlorid solution ranged in a series of 10 tubes from 1 to 10 to 1 to 5120. After adding the colloidal gold solution to each tube, as well as to a saline control, the mixture was incubated overnight at room temperature, when the final results were read. Complete decolorization of the fluid was noted as "5;" pale blue was read "4;" distinct blue as "3;" a color approaching lilac as "2;" and a bluish tint as "1." The "curves" given by the colloidal gold test with pathologic fluids are generally familiar to medical readers.

Relation of the Colloid Gold Reaction to Clinical Diagnosis. For this part of the study 700 cases were investigated. Of these there were 500 cases of neurosyphilis embracing 100 each respectively of early central nervous system involvement with primary or secondary syphilis, general paresis, tabes dorsalis, taboparesis, and diffuse cerebrospinal syphilis. This latter group includes vascular, meningovascular, and other types not falling into the other groups. As controls to this group 200 cases of syphilis without central nervous system involvement were used, namely, 100 cases of latent syphilis and 100 cases of hereditary syphilis. The diagnosis was made on all these cases from the clinical picture and other findings irrespective of the colloidal gold.

Lumbar punctures were performed as a routine measure on the patient's entrance to the clinic before any treatment was instituted. Care was taken in collecting specimens so that they did not come in contact with any substance which might give an untrue reaction. Any fluids containing blood have not been used as it has been shown by Black,[1] Kellert,[2] and others [3,4] that false reactions can be obtained.

For the sake of brevity and to do away with long columns of colloidal gold reactions, I have tabulated the curves, first, into the zones where the greatest color change takes place as suggested by Felton and Maxcy[5] and, second, by the maximum intensity of this color change in one or more tubes. For example, a curve of this nature 0012332100 would be placed in Zone II, opposite 3, in the column showing the degree of color change. This is somewhat similar to the method that Larkin and Cornwell[6] employed, except that they did not divide their curves into zones.

TABLE 1.—SPINAL FLUIDS OF 700 CASES OF VARIOUS TYPES OF SYPHILIS SHOWING ZONE OF COLLOIDAL GOLD REACTION AND MAXIMUM COLOR CHANGE.

Reaction Zone I = greatest precipitation in first tubes containing higher concentration of spinal fluid; *i. e.*, 55|54|32|10|00.
Reaction Zone II = greatest precipitation in middle tubes containing moderate concentration of spinal fluid; *i. e.*, 00|12|32|10|00.

	No. of cases.	Zone I. Numbers showing maximum color change.					Zone II. Numbers showing maximum color change.					Negative colloidal gold reaction.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
Early involvement of C. N. S. with active primary or secondary syphilis	100	5	3	5	3	6	..	3	24	22	19	10
General paresis	100	65	17	2	1	1	1	4	4	2	3	
Tabes dorsalis	100	6	4	1	..	..	..	13	34	20	18	4
Taboparesis	100	32	13	4	1	1	..	4	11	16	14	4
Diffuse cerebrospinal syphilis	100	5	8	2	1	2	..	10	25	20	26	1
Controls	...	..	..	..	..	..	..	..	..	..	..	..
Latent syphilis	100	..	..	..	1	5	..	..	4	10	44	36
Hereditary syphilis with no evidence of neurosyphilis	100	..	..	..	..	1	..	1	2	7	39	50

Latent and Hereditary Syphilis. As a control to the group of cases showing neurosyphilis, we have used 100 cases of syphilis which show no evidence of cerebrospinal syphilis or active visceral involvement, and also 100 cases of hereditary syphilis with no clinical central nervous system manifestations.

In the group of latent cases (Table 1), 36 were entirely negative while 49 showed a maximum color change of "1," which falls well within normal limits. Eleven cases had a color change of "2." Greenfield and Carmichael[7] also consider these slight reactions in normal limits. None of these cases had any suggestive evidence of cerebrospinal involvement on examination and their spinal fluids were otherwise entirely negative. Four cases of this group had a color change of "3." One of these patients had slightly hyperactive reflexes and another had slight inequality of the pupils. Both of these cases showed no further evidence of central nervous system involvement on subsequent examinations. Outside of this change in gold sol their spinal fluids were negative. The other 2 cases presented no abnormality on examination and their spinal fluid was otherwise negative.

Larkin and Cornwell[6] found in a group of latent syphilitics some cases having color changes as marked as "4." They[8] also found in epileptic patients 8 per cent with curves of "3" or higher. Miller,[9] Cockrill,[10] and Miller and Levy[11] all showed somewhat the same changes in similar groups. Warwick and Nixon[12] conclude that patients without syphilitic involvement of central nervous system give no colloidal gold curve, but one of their cases shows a curve of "3" and another one of "4."

In the congenital group 97 of these cases are within the usual normal range of reaction. However, here again one sees a few cases which have definite colloidal gold changes without any other confirmatory signs of nervous system involvement. The one case (Table 1) showing a precipitation of "4" had a syphilitic osteomyelitis of the frontal bones of the skull, but the neurologic examination was negative as well as the other spinal fluid findings.

In regard to these 2 groups of cases, the normal reaction could be considered to be "2" or less, but it should be kept in mind that from 3 to 4 per cent will show marked changes and the clinical and other laboratory examinations will be entirely negative.

Central Nervous System Involvement With Primary or Secondary Syphilis. All of the cases in this group at the time of the lumbar puncture showed active syphilis either in the primary or secondary stage. Also, most of them gave evidence clinically of some cerebrospinal involvement either by symptom, such as headache, dizziness or general malaise, or from examination, having either leukoderma colli, essential alopecia, hyperactive reflexes, or other signs of meningeal irritation. In many of the cases the cell count was extremely high, 200 to 300. The types of curves varied considerably, from

10 which were negative to 8 definitely of the so-called paretic type. Five more cases were also rather high in Zone I, having a color change of "3." This finding is most interesting when one considers that 13 per cent of these early cases gave colloidal gold curves usually associated with general paresis. A much larger group showed the rather high middle zone curve which is associated with diffuse involvement. There were 49 cases of this class.

Stokes[13] has found the paretic curve rarely in this type of case, but further states that it does not necessarily mean a paretic outcome. The outcome of these cases in this series will be further discussed under therapy. Solomon[14] also has found that most of the curves are weak, but that the stronger reactions are occasionally met with. Moore[15] in a very extensive article on early nervous system involvement in syphilis found a rather large group with a paretic type of curve. Fordyce[16] also states that it is frequently seen.

General Paresis. Since the introduction of the colloidal gold test it has been thought that a strong precipitation in the first tubes was nearly a uniform diagnostic finding in general paresis. Our results tend to bear this out for the most part in that 65 of the cases had a Zone I change with a maximum color change of "5," while 19 others presented the same type of curve but the maximum color change was of less intensity, "3" or "4." Nine cases gave slight changes which in view of the control series should be regarded as normal. Curves showing strong middle zone reaction also occurred in 9 cases.

In the latter 2 types most of the cases are early, with only slight mental deterioration. Under treatment only 2 later showed the typical high first zone reaction.

The incidence of "paretic" curves in paresis varies from 100 per cent found by Miller and Levy[11] to 84 per cent found by Rawlings.[17] Many others have reported on this type of syphilis and most of their reports average about 90 per cent typical curves. Thompson[18] in a large series, 639 cases, found 92.2 per cent high Zone I curves.

Differentiation of paresis into early and advanced types by Larkin and Cornwell[8] showed about 98 per cent of the advanced types had the "paretic" curve, while only 66 per cent of the early form showed this reaction. Our series is somewhat lower than that usually reported and this may in part be accounted for by the fact that we see many patients whose symptoms are of short duration and not particularly marked. Likewise reports from psychiatric institutions where a good deal of this work has been done would tend to be higher.

Tabes Dorsalis. The reactions found in this group are of much less intensity than found in general paresis. Forty-two cases gave normal reactions, 4 of them being entirely negative, 18 showing only a precipitation of "1" and 20 showing a precipitation of "2." The rather high middle zone curves usually considered typical of tabes was found in 47 cases, while the "paretic" type was noted in

11 cases. Of this latter group 4 changed from a "paretic" curve to a "tabetic" curve later under treatment.

It is most important to note that in this type of involvement one finds such a large percentage (42) having normal response in the colloidal gold. Larkin and Cornwell[6] in a small series of 22 cases had 50 per cent fall into this group. Greenfield and Carmichael[7] in a much larger series also found a high per cent (40) with normal curves. On the other hand, especially by earlier authors, tabes was considered to give a rather uniform type of reaction; some, such as Lee and Hinton,[19] reporting uniform high Zone II curves. As has been noted frequently before, this series presents also an appreciable number of "paretic" curves.

Taboparesis. One would expect to find the reactions of this group about midway between that of tabes and paresis, and such is the case. The number of high first zone curves are half the number that were found in general paresis, while there is marked increase of the number of weak reactions, 4 of the cases being entirely negative. There is a subsequent decrease of the strong middle zone reaction of the tabetic group.

Diffuse Cerebrospinal Syphilis. The reports on this type of nervous system involvement are varied, but they agree in the main that there is no characteristic reaction of the group, the middle zone type of reaction being met with most frequently. Nearly all showed some "paretic" curves. In the cases reported by Thompson[18] 50 per cent showed a "paretic" curve. He concludes that colloidal gold is of no value in differentiating between cerebrospinal syphilis and paresis. At the other extreme, Vogel[20] showed in his cases of cerebrospinal syphilis that the intensity of the reaction was less than his group of tabetic fluids.

In this series half of the reactions are within normal limits, the others being more intense and falling either in the first or second zone. There were 15 cases of the high Zone I type so frequently seen in paresis.

Discussion. From Table 1 one readily sees that no one type of neurosyphilis presents a constant colloidal gold curve, but that a wide variation occurs in each group. In the cases of general paresis the finding of a similar type of reaction is most frequent. Here 84 per cent of the cases gave a strong precipitation in the first zone, while the other 16 per cent gave weaker reactions and most of these in the second zone. The curves occurring in the other types of involvement showed nothing characteristic except that in a general way the tabetic and diffuse cerebrospinal cases tended to react in the second zone with a rather slight amount of precipitation. A diagnosis therefore from the colloidal gold alone is impossible. In general paresis where a characteristic curve occurs frequently, it may well be considered a confirmatory finding but one should not rule out this diagnosis if the curve is not typical. On the other hand,

the finding of strong precipitation in the first group of tubes does not necessarily imply paresis, as all of the groups of neurosyphilis showed some cases in which this was present. The taboparetics have the highest per cent of this type of curve, that of 32.

Because of this variance of the colloidal gold reaction in each type of syphilis, the use of the reaction as an aid to differentiating one type from another should be used with reservation and more reliance placed on the clinical picture.

The occurrence of a slight or even a fairly strong colloidal gold reaction in a patient who shows no clinical evidence of central nervous system involvement and in whom the spinal fluid remains negative except for this colloidal gold reaction on subsequent examination, should be regarded as normal for that individual. As has been shown in Table 1, 57 per cent of the cases without central nervous system involvement show precipitation in some tubes varying from "1" to as high as "4."

The Effect of Antisyphilitic Therapy on the Colloidal Gold Reaction. The changes in colloidal gold reaction were studied in 413 cases under treatment for neurosyphilis. Of this number, 127 were treated by intradural therapy, 138 by tryparsamide, and 148 by malaria. The number of spinal punctures done on each individual patient varied considerably. Some of the malarial patients had but 2 spinal punctures, 1 before and 1 after therapy, while some of the patients who received tryparsamide had as high as 29 punctures. The average number of spinal tests in the patients receiving intradural therapy or tryparsamide was between 7 and 10. After malaria therapy the average was 2 to 3. The reason for this small number is because many of the patients failed to return for check up examinations.

It is impossible to record all the changes noted in each individual case. The variation of one reaction to the next may be only a slight change in intensity, or may be marked with also a change in the zone of maximum reaction. Nearly all of the cases showed some differences from time to time. In attempting to determine the extent and number of the major fluctuations occurring in an individual case undergoing treatment, we have recorded the number of times that the colloidal gold shifts from one zone to the other. Also, we have recorded the difference in the maximum color reaction from the time treatment was started until it was stopped. For example, a patient starting treatment had a gold sol of 0012332110. At the end of treatment the gold sol was 0001110000. The difference of maximum color intensity in this case would be a decrease of 2. Not infrequently after therapy the gold sol would be more marked in its reaction and this is recorded as an increase in intensity. The amount of increase depends on the difference between the original test and the last one taken. No record has been made of the differences of intensity occurring after each individual treatment.

The cases receiving a certain type of therapy have been grouped according to their clinical diagnosis.

All of the cases reported have been treated by the department of dermatology and syphilology.

Intradural Therapy. One hundred and twenty-seven cases were treated by this method. Of this group 14 cases were early nervous system involvement having active syphilis at the time of the original examination. In addition there were 25 cases of general paresis, 24 cases of tabes dorsalis, 24 cases of taboparesis, and 40 cases of late diffuse cerebrospinal syphilis.

The method of intraspinal therapy is that originally described by Wile[21] in which arsphenamin (0.00025 gm.) is mixed directly with the spinal fluid and immediately reinjected. The patients receive these treatments weekly for a period of 4 weeks and then are given a rest period of 3 months. At the end of that time they receive another course, usually of two treatments. These were carried on as long as they were thought of value to the patient. Along with the intradural therapy, intravenous injections are given, also heavy metals, either bismuth injections or mercury inunctions.

Zone Change. As shown in Table 2, about half the cases in each group presented the same type of curve at the end of treatment as they had at the beginning. In the 14 cases of early nervous system involvement, 10 showed no zone shift and the remaining 4 shifted only once. All of these latter 4 cases had definite paretic curves to start with and later showed a shift from the first zone to the second and a marked decrease in the amount of precipitation in the individual tubes. This change occurred after only 3 to 4 treatments. There was 1 case which was originally of Zone I type and remained so at the end of 3 intradural treatments and some intravenous therapy. He failed to return for subsequent therapy so that the eventual outcome could not be determined. Except for this case, all of the others that showed no zone change were of the Zone II type. This rapid change from a strongly paretic curve to one within normal limits has been observed by Fordyce[16] in this type of case.

In tabes dorsalis, taboparesis and late diffuse cerebrospinal syphilis, a little over half the cases showed no zone change following intradural therapy (Table 2). Most of the cases that did have a change in zone reaction occurred only once or twice. However, the shift of one zone to another was noted 6 times in 1 case of tabes. The most frequent change in these cases was that of Zone I to the middle zone.

In general paresis which is usually considered the most constant of reactions, we found that less than half remained in the same zone in which they started. Here again there was tendency for the curves to become middle zone in type under therapy. This is not, however, a constant finding, some cases eventually shifting back to the original first zone type and remaining there at the cessation of treatment.

There is a considerable variance of opinion as to the persistence of paretic type of curve. Kaplan and McClelland[22] noted that the curve was stationary under treatment and considered it in the nature of a "Wassermann-fast" condition. Hammers[23] and Green[24] also noted changes only in a small group of treated cases. Thompson,[18] Swalm and Mann[25] on the other hand noted a definite tendency for the paretic type to become middle zone under therapy. Klerret[2] reported a case of taboparesis showing several shifts from one zone to another. Warwick[26] found only a few instances of zone change in her series, which is rather large. This article also contains an excellent review of the subject. Greenfield and Carmichael[7] state that under treatment the colloidal gold stays constantly paretic in general paresis except that there are occasional changes to the luetic zone due to irritation from interspinal treatment. We have seen this shift from a paretic to a middle zone curve so frequently, and in many cases in which the latter curve becomes constant, that it is difficult to feel that it is all explained on an irritation basis.

TABLE 2.—INTRADURAL THERAPY IN 127 CASES OF NEUROSYPHILIS SHOWING THE FREQUENCY OF ZONE CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Numbers representing frequency of zone change.						
		No change.	1.	2.	3.	4.	5.	6.
Early C. N. S. involvement with active syphilis	14	10	4					
General paresis	25	11	4	3	3	3	1	
Tabes dorsalis	24	14	4	3	1	1	1	1
Taboparesis	24	15	5	3	..	..	1	
Diffuse cerebrospinal syphilis	40	24	6	4	3	1	2	

TABLE 3.—INTRADURAL THERAPY IN 127 CASES OF NEUROSYPHILIS SHOWING AMOUNT OF COLOR CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Decrease in color. Numbers representing the amount of change.					Increase in color. Numbers representing the amount of change.					No color change.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
Early C. N. S. involvement with active syphilis	14	..	..	1	5	5	..	..	..	2	..	1
General paresis	25	..	..	3	2	5	..	..	..	..	2	13
Tables dorsalis	24	..	1	3	6	7	..	..	..	2	2	3
Taboparesis	24	..	..	5	2	6	..	..	.	..	4	7
Diffuse cerebrospinal syphilis	40	..	..	1	6	14	..	..	1	1	4	13

Color Change. In the majority of cases a decrease in the intensity of the reaction was noted (Table 3). For the most part this was

slight, the difference of maximum color being only "1" or "2" after treatment. One case of tabes showed the largest decrease, that of "4." The change in color cannot be expected to be very great when one considers that most of the cases before therapy showed the strongest precipitation as being "3" or less. Therefore a decrease in color even if the gold sol became perfectly flat could only be 3, or in the case of an original maximum precipitation of "2" a decrease on only 2 is possible. One would then expect the most marked changes of color intensity to take place in the group of general paresis where many of the fluids give readings of "5." This, as noted in Table 3, is not the case. Half of the cases showed no change at the end of therapy and this group corresponds nearly exactly with the group found in Table 2, which showed no zone shift.

The cerebrospinal group had one-third of the cases remaining stationary as to intensity of color reaction after treatment.

Each type of neurosyphilis presented a few cases in which there was a stronger color reaction following treatment than the patient presented originally. None of these increases in color could be interpreted as provocative in nature as described by Warwick and Nixon.[12]

In the treatment of 5 cases intraspinously, Vogel[20] notes a progressive flattening which was in accord with the clinical improvement and believes this to be a more objective indicator of improvement than the decrease in cells and globulin reaction. Many others have also noted the decrease in intensity of the color reaction. Warwick[26] concludes that there is a tendency for the reaction to decrease under antisyphilitic treatment, but she notes also that an increase can occur similar to what we have found in this series.

Tryparsamide Therapy. One hundred and thirty-eight cases were studied which received this type of treatment. Thirty-four of these were tabes, 35 general paresis, 19 taboparesis, and 50 late diffuse cerebrospinal syphilitics. The patients were treated in the following manner. Weekly injections of tryparsamide were given intravenously for six weeks and then there was a rest period of 2 months and the course was again repeated. Some of the patients received as high as 50 injections over a period of 2½ to 3 years. Along with the tryparsamide either mercury inunctions or intramuscular injections of bismuth salicylate were given. During the first course of treatment spinal drainages were performed after each injection. In the subsequent courses drainage was done only after every other injection.

Tables 4 and 5 dealing with tryparsamide therapy have been made up in the fashion as that described above and used in showing the changes under intradural treatment. Namely, the numbers of zone shifts have been recorded and also the difference in maximum color intensity before and after treatment.

TABLE 4.—TRYPARSAMIDE THERAPY IN 138 CASES OF NEUROSYPHILIS SHOWING THE FREQUENCY OF ZONE CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Numbers representing the frequency of zone change.											
		No change.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
General paresis .	35	11	9	3	3	3	3	1	..	..	2		
Tabes dorsalis .	34	18	7	5	2	..	..	..	1	..	1		
Taboparesis . .	19	12	4	1	..	2							
Diffuse cerebro-spinal syphilis	50	24	7	6	4	4	..	2	1	1	..	..	1

TABLE 5.—TRYPARSAMIDE THERAPY IN 138 CASES OF NEUROSYPHILIS SHOWING AMOUNT OF COLOR CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Decrease in color. Numbers representing the amount of change.					Increase in color. Numbers representing the amount of change.					No color change.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
General paresis . .	35	..	3	2	8	8	..	..	..	..	2	12
Tabes dorsalis . .	34	..	..	3	5	13	..	1	1	1	4	6
Taboparesis . . .	19	..	..	1	1	5	..	..	..	1	5	6
Diffuse cerebrospinal syphilis	50	..	..	4	5	11	..	..	..	1	8	21

Zone Change. The shift from one zone to another was frequently met with in all types of cases in this series. However, the cases of general paresis were the only ones in which more than half showed some shift. In this group only about one-third remained in the same zone in which the maximum reaction occurred before treatment. There were a large number which changed from a "paretic" to a middle zone reaction and remained that way during treatment. Two cases shifted from one zone to the other 9 times. The taboparetic group was the most stable during treatment, 12 of the 19 cases remaining unchanged, and the highest number of shifts noted in this group was four.

The tabetic and cerebrospinal cases presented similar pictures, about half of the cases in both groups remaining stationary. One of the cerebrospinal cases oscillated back and forth from one zone to the other 11 times. This case before treatment showed a Zone II reaction and finally at the end of treatment presented a similar type of curve.

Color Change. The maximum color change was decreased or increased in a majority of all the groups of cases, as shown in Table 5. The cerebrospinal group showed less change than the others, 21 cases out of 50 remaining unchanged. All but 6 of the 34 tabetic cases showed either a decrease or increase in the intensity of the

reaction. About one-third of the paretic and cerebrospinal cases remained unchanged.

The group of general paresis that showed no color change corresponds nearly exactly to the group which had no zone change. These cases were of the typical "paretic" type (marked precipitation in the first part of the curve). A similar group was found in the cases treated by intradural therapy.

As in the cases receiving intradural therapy the decreases in color was for the most part slight. The most marked change in this respect was seen in 3 cases of paresis in which the decrease was that of "4."

There was a stronger reaction at the end of treatment in a considerable number of each group. Six of the taboparetics or one-third of the total number showed an increase, while only 2 cases of paresis had more intense reactions at the end of therapy.

Since the advent of tryparsamide there has been considerable difference of opinion as to its effect on the spinal fluid as well as its general therapeutic value in neurosyphilis. Lorenz, Loevenhart, Blechwenn and Hodges[27] reported marked improvement in colloidal gold under this type of therapy. Many of the initial "paretic" curves became luetic in type. A relatively large number became entirely negative. Similar improvement was noted by Moore, Robinson and Lyman[28] and Moore, Robinson and Keidel.[29] Flattening out of the "paretic" curve was also observed by Carr.[30] Fong[31] in his series of cases found none that became negative but the majority showed some reduction in intensity.

On the other hand, Ebaugh and Dickson[32] found the serologic changes meager and transitory. Wile and Wieder[33] occasionally noted certain minor changes, but the "paretic" curve remained so after therapy. Only slight, indefinite responses were also found by Solomon and Viets,[34] Banford,[35] and Foster.[36]

Malaria Therapy. This group includes 148 cases of neurosyphilis which were treated by malaria. Of these 4 had early nervous system involvement with active primary or secondary syphilis, 73 general paresis, 13 tabes dorsalis, 32 taboparesis and 26 with late diffuse cerebrospinal syphilis. All of these cases were punctured immediately before inoculation with the plasmodium and again as soon after the chills had been stopped as was practical. A number of the patients failed to return for a check up so that there is only a record of two punctures in some cases. The others returned at intervals of 3 months for subsequent check-up examinations and lumbar punctures. In the interim some of them received heavy metals, either mercury or bismuth. The zone changes and the differences of the maximum color reaction have been tabulated (Tables 6 and 7) similar to the cases that received intradural and tryparsamide therapy. All cases have been used, those receiving only two punctures and those having more than that number.

TABLE 6.—MALARIA THERAPY IN 148 CASES OF NEUROSYPHILIS SHOWING THE FREQUENCY OF ZONE CHANGE IN THE COLLOIDAL GOLD REACTION.

	Numbers representing the frequency of zone change.				
	No. of cases.	No change.	1.	2.	3.
Early involvement with active syphilis	4	4			
General paresis	73	41	25	4	3
Tabes dorsalis	13	9	4	1	
Taboparesis	32	18	10	3	1
Diffuse cerebrospinal syphilis	26	17	5	4	

TABLE 7.—MALARIA THERAPY IN 148 CASES OF NEUROSYPHILIS SHOWING AMOUNT OF COLOR CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Decrease in color. Numbers representing the amount of change.					Increase in color. Numbers representing the amount of change.					No color change.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
Early involvement with active syphilis	4	..	1	..	1	1	..	..	..	..	..	1
General paresis	73	1	1	4	18	11	..	..	..	..	5	33
Tabes dorsalis	13	..	..	..	2	5	..	..	..	..	6	1
Taboparesis	32	..	..	5	2	8	..	..	..	2	4	11
Diffuse cerebrospinal syphilis	26	..	..	1	7	7	..	..	..	..	3	8

Zone Change. The shift from one zone to another is less marked in the malarial-treated group than in the other forms of therapy. This may in part be accounted for by the fact that there are no long series of punctures, the most that one patient received being eight. Well over half of the cases in each type of neurosyphilis showed no zone change. In the cases with active syphilis all of them remained the same. Three of the cases had Zone I curves and the other a Zone II type.

Approximately two-thirds of the tabes and taboparetics stayed stationary. Of the cases showing a shift of zone none of them were very marked. Three cases of general paresis shifted 3 times and 1 case of taboparesis shifted once. O'Leary[37] found many cases of paretics in which there was a change to Zone II type of curve and also that this was more frequent in malaria than with the other types of therapy.

Color Change. The color change from the maximum intensity noted before treatment to that after treatment is striking. All but one of the tabes cases showed some change, while the others with

the exception of the paretics showed a difference in two-thirds to three-fourths of the cases. In the group of general paretics well over half had a decrease or increase after malaria.

The amount of decrease in the precipitation of the colloidal gold is more marked with this type of therapy than with the others. Two cases showed a reduction of "4," while one case of paresis changed from a maximum color reaction of "5" to "0." This is a more marked change than has been found in either of the other two types of treatment.

An increase of color reaction at the end of therapy was noted again in a small group.

The effect of malaria on the colloidal gold has been considered slight by Huston and Armstrong,[38] and Carr.[30] Ferraro and Fong[39] agree that it is more resistant than the Wassermann and other reactions, but they make the further observation that, while the colloidal gold changes only little at first, at the end of 3 years there is an improvement in about 85 per cent of paretics and a few in which they become negative.

Therapy by Spinal Drainages Only. A small group of patients who had received no antisyphilitic therapy were given a series of spinal drainages. These were performed 2 or 3 times a week for 2 weeks so that in all they received from 4 to 6 spinal punctures. This was done to determine what change would take place in the colloidal gold without any definite antisyphilitic treatment. This group is so small that the results cannot be conclusive but one finds some interesting changes. There was 1 case of general paresis which showed a Zone I reaction with a maximum precipitation of "5." This remained constant in a series of 5 drainages. In 1 case of tabes and 1 case of diffuse cerebrospinal syphilis the zone of reaction remained the same, but there were slight differences of maximum color change noted from one drainage to the other and also the number of tubes showing color changes varied. A case with active secondary lesions and an early central nervous system involvement showed only slight color changes. The most striking changes were noted in 2 cases of taboparesis. One of these started with a strong Zone I curve, which upon subsequent examination varied in intensity, and after the third lumbar puncture shifted to a Zone II curve with a maximum color change of "3." The other case first presented a Zone II type of curve, which on the next examination shifted to a strong Zone I reaction. The following 3 examinations revealed the same type of reaction. The fifth colloidal gold reaction was again identical with the original.

The fact that in this small series the patients having taboparesis showed the most marked change does not necessarily mean that it is characteristic of this type of involvement. Similar changes have been noted in other types of syphilis where repeated spinal punc-

tures have been done without treatment. However, in this series the changes noted in the other types of syphilis were slight.

In advanced cases of general paresis which have been committed to the University Psychopathic Hospital, the colloidal gold curves that have been taken at intervals without treatment tend to remain similar, but occasionally one finds a case in which there is a change both of zone of reaction and the amount of precipitation.

From this small series of cases it is obvious that the colloidal gold is by no means stable in its reaction and that it varies from time to time in an individual case which is not receiving any specific treatment. For the most part these changes are so slight as to be negligible but marked differences do occur, as was noted in the 2 cases of taboparesis.

Discussion. The changes in the colloidal gold reaction found after any type of antisyphilitic therapy present a confusing and inconclusive picture, as is noted from the tables showing the effect of treatment. Changes similar to those found with treatment may occur when only a series of spinal punctures are performed in the absence of all other therapy. This was noted particularly in 2 cases of taboparesis in which this was done. If one attempts to consider reduction or zone change of the colloidal gold as of prognostic significance, it should be done guardedly, realizing that marked changes can occur in a short time after the original examination without any intervening therapy. However, there is a tendency for Zone I curves to change to the middle zone in all types of treatment and for Zone II curves to remain so. This is not characteristic of any special kind of therapy but occurs frequently with all types.

In a general way one can say that under treatment there is a reduction in the maximum color intensity and that the amount of reduction is about the same in all types of therapy. Under malarial treatment it was a little more pronounced and here one finds the greatest decrease in any one individual case.

A very interesting finding with each type of treatment was that in a small group of cases there was an increase in maximum color change after treatment. Usually these increases were slight but one case of tabes dorsalis undergoing tryparsamide treatment showed an increase of "4." No definite explanation for this can be made out. Other workers have also found this increase after treatment and were unable to find any correlation between it and the clinical course of the patient. Apparently it has no significance as far as being an indication of retardation of improvement.

About a third of the cases receiving intradural and tryparsamide therapy presented the same color change at the end of therapy as they had at the beginning. The cases receiving malaria had a slightly larger group which did not change. This is somewhat surprising in that the most striking clinical improvements are

noted in this group and if the colloidal gold tended to follow the clinical course one would expect to find a decrease of precipitation paralleling their improvement.

Under each type of treatment there was a group of general paretics which showed no change in zone of reaction and this group closely paralleled those which showed no color change. They remained fixed throughout treatment. Many of these cases did not improve under treatment but there were some, especially those treated with malaria, where clinical improvement occurred with no change in the colloidal gold. No other type of central nervous system involvement presented as large a group in which the curve stayed the same throughout treatment.

Conclusions. 1. Syphilitics without central nervous system involvement frequently show some changes in the colloidal gold curve. Usually the color change is not over "2" but stronger reactions do occur.

2. No one type of neurosyphilis presents a constant curve.

3. In general paresis a strong Zone I curve is found in a high percentage of cases.

4. A strong Zone I curve does not necessarily mean general paresis as it is found in all types of neurosyphilis.

5. A middle zone curve is not of diagnostic significance as it occurs frequently in all types of neurosyphilis.

6. No type of antisyphilitic therapy produced changes in the colloidal gold with enough uniformity to merit prognostic significance.

7. The zone of reaction changes frequently and this may occur many times under treatment.

8. Decrease of maximum color reaction is commonly met with following treatment, but increase of color reaction also occurs and these changes do not parallel the clinical course.

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CHRONIC ADULT IDIOPATHIC TETANY. REPORT OF A CASE.

By Simon S. Leopold, M.D.,
ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA,
AND
Leon Jonas, M.D.,
WOODWARD FELLOW IN PHYSIOLOGIC CHEMISTRY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Medical Division and the William Pepper Laboratory of the University of Pennsylvania.)

For clinical purposes tetany may be divided into the following types: (*a*) Infantile; (*b*) postoperative; (*c*) gastric; (*d*) hyperpneic, and (*e*) idiopathic.

The infantile type is the most common. It occurs most frequently during the so-called tetany months, March and April, the result chiefly of insufficient exposure to sunlight, and consequent vitamin D deficiency during the winter.

The postoperative type follows accidental removal, injury to, or occlusion of circulation to the parathyroids, usually occurring during extirpation of the thyroid gland.

The gastric and hyperpneic types are due to alkalosis.

Nothing can be said with certainty regarding the etiology of idiopathic tetany. All types of tetany except those due to alkalosis have one feature in common, a marked reduction in the blood serum calcium. In the tetany of alkalosis the blood serum calcium is normal. In adults, tetany is usually observed either as a post-operative condition, following thyroid surgery, or as the result of alkalosis from certain high obstructive lesions of the gastrointestinal tract.

In this communication, we are concerned chiefly with chronic idiopathic tetany, which, as its name implies, is a type of tetany for which no accepted cause has been established. The extreme rarity of this condition, particularly in adult males, has been emphasized by Liu,[1,2] who cites a single case in a Chinese male, aged 46 years, which is almost a prototype of ours. A few cases have been reported in females. We have not accepted a great many recorded cases considered to be idiopathic tetany in adult males for reasons which appear to us to be adequate.

A critical analysis of the literature suggests that the infantile type of tetany occurs also in adults. It is our belief that many of these cases, reported as adult idiopathic tetany, conform in all essential respects, to the infantile type. For example: Falta and Meyers[6] quote 528 cases of occupational idiopathic tetany in males, collected by von Frankl-Hochwart, of whom 223 were cobblers and

117 tailors. The symptoms of tetany in this group became manifested chiefly in March and April, with spontaneous remissions during the rest of the year. Obviously, their indoor occupation and seasonal incidence suggests that these cases are similar to the infantile type, due to vitamin D deficiency, from insufficient sunlight, diet poor in vitamin D, or both. They should not be called idiopathic tetany.

McCarrison[7] has described a form of so-called epidemic tetany observed in natives of the Himalayas, in association with epidemic goiter. One would infer that tetany in these cases results from parathyroid deficiency which might be associated with epidemic goiter. However, where epidemic goiter is extremely prevalent, as in the Austrian Tyrol and Switzerland, associated tetany is excessively uncommon. Moreover, McCarrison states that when the Himalayans with epidemic tetany and goiter move to a different locality, spontaneous recovery from tetany occurs. It is therefore apparent that this so-called epidemic tetany of the Himalayans is not due to parathyroid deficiency associated with goiter, but to environmental factors, incident to diet and climate. It may likewise be concluded that these cases are similar to the infantile type and a secondary rather than an idiopathic tetany.

If, therefore, we are justified in our opinion, that these cases reported by von Frankl-Hochwart and McCarrison are not true idiopathic tetany in adult males because these and many others so reported have a demonstrable etiology, it is apparent that this cryptogenetic type is sufficiently unusual to recommend the report of the following case.

This patient, studied over a period of 4 years, had no seasonal remission of symptoms, no surgical operations, no symptoms or signs of any obstructive lesion of the gastrointestinal tract and no clinical or chemical evidences of alkalosis.

Case Report.—L. B., male, white, aged 38 years, first came under our observation in April, 1927. For the previous 6 months he had noted peculiar muscle spasms in the hands and arms with muscle cramps and undue fatigue in the legs, aggravated by any muscular effort. He described numerous attacks of sudden, momentary, complete loss of voice and difficulty in breathing. At such times before phonation became possible he noticed a loud crowing inspiratory stridor, and following this, speech was audible but very husky. He also described numbness and parasthesias of the hands, arms and legs, and noticed that frequently, when his arms were resting on a chair or on a desk, his hands would involuntarily go into spasm, with the thumbs drawn into the palms. He also described sudden attacks of transient diplopia which could be relieved by covering one eye, unaccompanied by either headache or vertigo. Parasthesias, muscle spasms and ocular symptoms occurred every day; loss of voice, many times a day. Apart from these unusual symptoms, there were no other complaints. Gastrointestinal symptoms were conspicuously absent and there had been no loss of weight. The patient exhibited no apprehension about his condition, regarding it in a detached, but interested sort of way. One year later diarrhea ensued with 5 or 6 liquid stools daily. A less pronounced diarrhea

has persisted until the present time, unaccompanied by anorexia, nausea or vomiting. At the time of his first examination he had attained his maximum weight (155 pounds) and this has remained practically constant.

The previous medical history was unimportant except for an attack of uncomplicated scarlet fever in childhood. There was no history of previous operations, on the neck or elsewhere, no history indicative of rickets or tetany in childhood, no unusual dietary habits and no history of acute or chronic gastrointestinal disease. No other members of the patient's family had or has similar symptoms. He conducted an advertising business, was outdoors a considerable part of each day, walked a great deal and played golf 3 or 4 afternoons a week in season.

Physical examination was essentially negative except for manifest evidences of tetany. Trousseau's and Chvostek's signs were positive, and the electrical reactions were those of tetany.

The following table tabulates the various therapeutic agents employed together with blood chemical studies before and during treatment.

THE VARIOUS THERAPEUTIC AGENTS EMPLOYED, WITH BLOOD CHEMICAL STUDIES, BEFORE AND DURING TREATMENT.

Date.	Treatment.	Blood serum.		Plasma.	
		Ca.	P.	NaCl.	CO_2.
April 25, 1927	None	5.8	5.4	...	74
February 15, 1928	Ca. lactate, gm. ij	6.1			
February 23, 1929	Ca. lactate, gm. vj	6.4	6.7	570	69
July 20, 1929	Ca. lactate, gm. vj; thyroid, gm. 0.2	6.4			
October 16, 1929	Ultraviolet radiation	7.1	6.8		
November 19, 1929	Viosterol, gtts. xx	6.8	5.9		
January 16, 1930	Viosterol, gtts. xxx	6.3	6.0	570	71
May 28, 1930	Parathormone 20 units (4 doses)	7.8	4.2		
November 10, 1930	Parathormone 20 units (6 doses)	8.3	5.0		
April 16, 1931	Parathyroid transplant, March 4, 1931	6.4	6.6		

In addition to these figures, isolated determinations were made of the blood pH, which was normal, of the basal metabolic rate which varied from −5 to −26 per cent, and of the gastric contents, the maximum figures of which were normal for free and total acidity.

Treatment with calcium lactate by mouth was begun in April, 1927, and except for brief intermissions, in order to evaluate the results of other therapy, has been continued to the present time. Two to 6 gm. per day have been administered. For a brief period of time this therapy was reinforced first by thyroid, gm. 0.2 daily and later by thyroxin gr. $\frac{1}{100}$ 3 times a day.

It was thought that the coincident low metabolic rate might have had some relationship to the parathyroid deficiency, because in hyperthyroidism there is an increase of calcium excretion while in myxedema it is decreased. However, Aub, Bauer, Heath and Ropes[8] have shown that the level of serum calcium is no indication of the rate of calcium metabolism.

Our patient showed no evidence of myxedema. Whether the deficiency of parathyroid secretion is related to hypofunction of the thyroid cannot be proved, although it seems quite suggestive. Our data likewise showed

that thyroid feeding had no effect on the level of the serum calcium. Its influence on the calcium balance could not be studied because the patient was ambulatory.

In August, 1929, the patient stopped all oral medication and received 8 treatments of ultraviolet radiation, twice a week for 4 weeks. Following this, in October, 1929, viosterol was prescribed in doses of 20 drops daily; in December, this was increased to 30 and during February and March, 1930, the patient consumed 60 drops of viosterol each day. In May, 1930, he was given 20 units of parathormone daily for 4 days and in October, 1930, 20 units of parathormone was administered every other day for 6 days, at the end of which time, blood chemical studies were made.

In March, 1931, a normal parathyroid gland was removed by Dr. Charles H. Frazier from a patient with hyperparathyroidism and transplanted by Dr. Ulrich into the rectus muscle of our patient. The gland removed was identified as normal parathyroid tissue by frozen section of a small fragment before being transplanted.

Results of Treatment. The use of calcium lactate by mouth, produced immediate amelioration of symptoms with partial freedom from laryngismus and spasms of the extraocular muscles. Undue fatigability and cramps in the arms and legs have persisted. Abstinence from calcium for 48 hours was followed by immediate recurrence of all symptoms with their customary severity. Although the intravenous administration of large doses of calcium will temporarily relieve the tetany following thyroparathyroidectomy, evidence is lacking of its good effect in latent tetany of either the infantile or adult types. In 3 patients reported by Liu, 2 juveniles and 1 adult, there was neither symptomatic relief nor elevation of either the diffusible or nondiffusible blood serum calcium.

The addition of thyroid, later thyroxin, caused no demonstrable effect on his tetany but raised his metabolic rate. Ultraviolet radiation produced temporary relief of symptoms to the point where no calcium was required for 3 weeks after the course of treatment was completed. The symptoms then returned.

Viosterol, even in doses of 60 drops a day, was so completely without beneficial effect, that the patient was compelled to reinforce it with calcium, in order to remain in reasonable comfort.

Regarding viosterol, it may be said that strikingly favorable results have been reported by Hess and Lewis,[9] and Gleich and Goodman[10] in the treatment of infantile tetany by this drug, comparable to the results obtained by cod liver oil and ultraviolet light. Other workers have confirmed this opinion, so that it can confidently be stated that viosterol acts as a specific in infantile tetany.

The efficacy of viosterol in the treatment of other types of tetany is very questionable. In the experimental animal, using thyroparathyroidectomized dogs, Urechia and Popoviciu[11] and Greenwald and Gross[12] were unable to raise the blood serum calcium with viosterol. Hess and Lewis failed in monkeys, concluding from this that viosterol acted by stimulating the parathyroids.

Brougher,[13] and Jones, Rapaport and Hodes[14] on the other hand, report conspicuous elevations in blood serum calcium, and the latter observed an extraordinary hypercalcemia in one of his operated dogs, following the administration of viosterol.

Brougher,[13] Hottinger[15] and Stern[16] have recorded favorable

results from the use of viosterol in human adult tetany. Brougher's most favorable result was in a patient with gastrointestinal tetany, which followed formidable resections of the small intestine.

He further reports its use in 4 cases where tetany followed subtotal lobectomy. Symptomatic relief was obtained but no figures for blood serum calcium are cited in these cases.

Liu failed utterly to relieve his case of idiopathic tetany with viosterol and there was no alteration in the blood serum calcium from its use.

We are unable to explain the symptomatic relief in our patient from the use of calcium. His improvement was not reflected in a conspicuous alteration of the blood serum calcium, although our studies do not include its fractionation into its diffusible and nondiffusible components. Perhaps an elevation of diffusible calcium could have been demonstrated but it could not have been conspicuous, as the total blood serum calcium was never raised above the tetany level, except upon the addition of parathormone.

Similarly, we do not know why ultraviolet radiation was symptomatically beneficial, especially since it apparently did not alter the fundamental state.

Uniformly good results ensue from the use of viosterol in infantile and juvenile tetany and in those forms of tetany in adults, erroneously called idiopathic, but more properly regarded as of the infantile type. In both the experimental animal and in adult humans, tetany induced by thyroparathyroidectomy has been relieved in some cases, in others it has failed completely. Its use in spontaneous idiopathic tetany failed in a single recorded case, that of Liu's, as it failed in ours.

It is reasonable to conclude that there may not only be a difference between thyroparathyroidectomized animals and man, but that there is even greater difference between the tetany in man occurring postoperatively and that which occurs spontaneously, as the idiopathic type. The absence of the thyroid in the postoperative type, and its presence in the idiopathic type may be very significant.

Of the various therapeutic measures employed, parathormone alone was capable of conspicuously elevating the blood serum calcium. During its use, and for a very short time thereafter, there was complete symptomatic relief, and complete though temporary abolition of the tetanic state.

Numerous attempts have been made to prevent or cure tetany in man by parathyroid transplantation. Borchers[17] reports 5 cases of postoperative tetany so treated, all of which were observed for several years after operation. One patient had recurrence of tetany after $2\frac{1}{2}$ years—the remaining 4 were not completely cured but obtained very appreciable relief.

In our case, after 6 weeks, parathyroid transplant failed com-

pletely either to alter the fundamental tetanic state or to raise the serum calcium above the tetany level. A superficial wound infection at the site of the transplant probably killed the graft.

Summary and Conclusions. 1. Evidence is presented to indicate that the infantile type of tetany resulting from vitamin D deficiency may be observed in adults, from the same cause. Most of the cases of so-called chronic idiopathic tetany in adults reported in the literature belong to this infantile type, and should be so considered.

2. Chronic adult idiopathic tetany, especially in males, is an excessively rare disease. A patient is reported in whom this diagnosis is justified by the exclusion of all recognized causes for this condition.

3. We have had the opportunity over a period of 4 consecutive years to observe, clinically and by laboratory studies, the effects of various forms of therapy. Calcium lactate by mouth for some unknown reason produced symptomatic relief but failed completely to raise the serum calcium above the tetany level. Viosterol was totally ineffective. Thyroid feeding was followed by an elevation of the subnormal metabolic rate but had no effect either on the tetany or on the serum calcium. Parathormone, subcutaneously administered, produced complete relief of tetany and elevation of the serum calcium above the tetany level during the period of its use. Parathyroid transplant failed completely because the graft probably did not remain alive.

4. The specific effect of parathormone and the total failure of all other therapeutic agents to alter the fundamental state suggest that, in this case at least, chronic tetany resulted from hypoparathyroidism. There are no reports available of histologic studies, ante-mortem or postmortem, of the parathyroid glands in chronic adult idiopathic tetany, hence the pathologic anatomy of this disease is entirely unknown.

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REVIEWS.

INTRODUCTION TO THE HISTORY OF SCIENCE, VOL. II. From RABBI BEN EZRA to ROGER BACON (Parts I and II). By GEORGE SARTON, Associate in the History of Science, Carnegie Institution of Washington. Pp. 1251. Baltimore: The Williams & Wilkins Company, 1931. Price, $12.00.

IT is impossible to avoid superlatives in writing of this stupendous work, properly called "one of the major intellectual undertakings of the century." In Volume I, which appeared in 1927, the unusual nature and wide purpose of the work, begun in 1912, was explained. Each chapter devoted to a given period of varying length began with a summary of the main facts, constituting a short account of the development of science during that period. These with the introductory chapter were the only parts intended for continuous reading, the larger remainder being like a huge *catalogue raisonné* intended for reference and study. The ambitious purpose of the whole is to present and explain the whole development of science, that is, "systematized positive knowledge." The importance of such a task, especially when it concerns "the only human activity which is truly cumulative and progressive," will be readily granted. More doubt might be felt about the ability of any one individual to accomplish it, but few could foretell the astonishing industry and productivity of Dr. Sarton, who must truly have lived for his task and for but little else in the past 20 years.

Volume I covered from the dawn of Greek and Hebrew science through the time of Omar Khayyam. Egypt, Mesopotamia and other possible dawn spots were not included, both on account of the difficulties in the way of strict chronological arrangement and the author's professed lack of sufficient philological and archeological equipment. The second volume, covering the 12th and 13th centuries from Rabbi ben Ezra to Roger Bacon, has on account of its bulk been divided into 2 books but with continuous pagination and one index for both. Following an explanatory preface comes an introductory chapter of over 100 pages, which is a book in itself, presenting a survey of the thought of the 2 centuries on the 8 or 10 major branches of science. Next come 4 "books," one for each half-century, each divided into 13 or 14 chapters on a Survey of Science and Intellectual Progress, Religious and Philosophical and Cultural Backgrounds, the Translators, Education, the individual sciences and an appendix. As the 4 surveys are much the largest of these chapters (totaling another 275 pages), it results that more

than a third of Volume II is devoted to a connected line of thought and expression, not unrelieved by pleasing flights of fancy and dignified humor. In the mountains of scientific data, the names of individual scientists or scientific details can be easily found with the help of one large index of 109 pages. Thus Hippocrates appears, even in this volume, 37 times; Hunain b. Ishaq, 38; St. Thomas Aquinas, 51; Roger Bacon, 63 and Maimonidez, 70 times. As an example of the author's thoroughness, he has spent "much time and energy in the study of Arabic and Hebrew" in the past few years, to improve his knowledge of these languages and cultures and the results are apparent in the printed book. And yet, feeling his knowledge inadequate to allow him sufficient penetration of Jewish and Muslim minds, he is spending the present year in the East for further intensive study. This will shortly bear fruit in a Prolegomena to the history of science which will be even more complete than the Introduction of these 2 volumes. While the index of this volumes makes the work an excellent lexicon, and bibliographic details, occupying 15.7 per cent of the whole, make it an excellent bibliography of the science of the period, nevertheless the author rightly emphasizes its synthetic qualities and prefers to look upon it as "a scientific map with full indications of sources."

Just as Volume II, covering two centuries, is considerably larger than Volume I, covering 20, so the ever increasing stream of science will constantly add to difficulties of accomplishment. Nevertheless, the author rightly feels that he should be able so to indicate the path that other trained scholars will carry out the plan when he lays down the burden. His astonishing productivity leads us to hope that he may so far continue the work that the task of the others will be slight. In any case, what he has already accomplished ensures his fame as an historiographer. Every scientific library must possess this work and many individuals will choose to do so, especially as the aid of the Carnegie Institution has kept the price remarkably low. We have no adverse criticisms, and if we had, in the light of the above, would consider it presumptuous to offer them. E. K.

LEZIONI DI MEDICINA BIOLOGICA. By C. MARTELLI. Pp. 548; illustrated. Naples: Edizioni Rinascenza Medica, 1930.

THIS is a collection from *Rinascenza Medica* of 66 articles by some 30 or 40 Latin authors, writing in Italian. There is a wide range of subjects, for instance, the first 11 are on medical philosophy, dermatology, tuberculosis, pathologic anatomy, surgery, acidosis, hematology and cancer (3). The approach is predominantly clinical. Attractions are the inexpensive but artistic binding, the inclusion of the author's portrait at the head of each article and a two to four

line summary beneath the title. Beyond making these articles somewhat more available, we fail to see much useful purpose in the publication. E. K.

A Clinical Study of Addison's Disease. By Leonard G. Rowntree, M.D., and Albert M. Snell, M.D., Division of Medicine, The Mayo Clinic and The Mayo Foundation. Pp. 317; 41 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $4.00.

The recently discovered cortical hormone by Swingle and Pfiffner fortunately was available for use by the authors. This with the surprisingly large material available, and the skillful handling of the many aspects of the problem, make it an extremely valuable contribution. The 50 pages devoted to the history of the subject and to Addison's original cases give a background which should be emulated by more writers on clinical subjects. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Electrotherapy and Light Therapy. By Richard Kovács, M.D., Clinical Professor and Director of Physical Therapy, Polyclinic Medical School and Hospital, New York. Pp. 528; 211 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $6.50.

History of Medicine in the Province of Quebec. By Maude E. Abbott, B.A., M.D. Pp. 97; 41 illustrations. Montreal: Medical Museum, McGill University, 1931. Price, $3.00.

Living the Liver Diet. By Elmer A. Miner, M.D., Independence, Kansas. With Introduction by William P. Murphy, M.D., Instructor in Medicine at the Harvard Medical School, Boston. Pp. 106; 3 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $1.50.

Growth in Private School Children. By Horace Gray, Stanford University Hospital, San Francisco, and J. G. Ayres, The Institute for Juvenile Research and Behavior Research Fund, Chicago. Pp. 282; illustrated with figures and tables. Chicago: University of Chicago Press, 1931. Price, $3.50.

The Use of the Self. By F. Matthias Alexander, with an Introduction by Professor John Dewey. Pp. 143. New York: E. P. Dutton & Co., Inc., 1932. Price, $2.00.

Female Sex Hormonology. By William P. Graves, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School, Surgeon-in-Chief to the Free Hospital for Women and to the Parkway Hospital, Brookline. Pp. 131. Philadelphia: W. B. Saunders Company, 1931. Price, $3.50.

Introduction to the History of Science, Vol. 2, From Rabbi ben Ezra to Roger Bacon (Parts 1 and 2). By George Sarton, Associate in the History of Science, Carnegie Institution of Washington. Pp. 1251. Baltimore: The Williams & Wilkins Company, 1931. Price, $12.00. See review page 425.

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A Doctor of the 1870's and 80's. By WILLIAM ALLEN PUSEY, Sometime President of the American Medical Association and of the American Dermatological Association. Pp. 153; illustrated. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.00.

A Nonsurgical Consideration of Prostatic Enlargement. By EDWIN W. HIRSCH, Associate in Urology, College of Medicine, University of Illinois; Urologist, Englewood Hospital, Chicago. Pp. 79; 6 illustrations. St. Paul, Minnesota: Bruce Publishing Company, 1931. Price, $2.00.

History of Medicine in the United States, Vols. 1 and 2. By FRANCIS R. PACKARD, M.D., Editor, Annals of Medical History. Pp. 1323; 103 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $12.00.

Imhotep to Harvey. Backgrounds of Medical History. By C. N. B. CAMAC, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University. Foreword by HENRY FAIRFIELD OSBORN, SC.D., LL.D. Pp. 324; 2 illustrations. New York, Paul B. Hoeber, Inc. Price, $3.75.

Allergy and Applied Immunology. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 359; 20 illustrations and numerous tables. St. Louis: The C. V. Mosby Company, 1931. Price, $4.50.

Manual for the Jewish Diabetic. By WILLIAM S. COLLENS, B.S., M.D., Assistant Chief, Diabetic Clinic, United Israel Zion Hospital. Foreword by HENRY JOACHIM, M.D., Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn. Pp. 138; 21 illustrations. New York: Bloch Publishing Company, 1931.

Medicine in Virginia in the Eighteenth Century. By WYNDHAM B. BLANTON. Pp. 449; illustrated. Richmond: Garret & Massie, Inc., 1931. Price, $7.50.

Nutrition Abstracts and Reviews, Vol. 1, Nos. 1 and 2, October, 1931. Pp. 351. Aberdeen: The Aberdeen University Press, Ltd., 1931. Price, 13 shillings.

Courts and Doctors. By LLOYD PAUL STRYKER. Pp. 236. New York: The Macmillan Company, 1932. Price, $2.00.

A Radiological Study of the Para-nasal Sinuses and Mastoids. By AMÉDÉE GRANGER, K.C.B., K.C.I., M.D., F.A.C.R., Professor of Radiology, Louisiana State University Medical Center; Director of the Department of Radiology, Louisiana State Charity Hospital, New Orleans. Pp. 186; 113 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $5.50.

NEW EDITIONS.

Varicose Veins. By H. O. MCPHEETERS, M.D. F.A.C.S., Director of the Varicose Vein and Ulcer Clinic, Minneapolis General Hospital. Pp. 285; 62 illustrations. Third edition revised and enlarged. Philadelphia: F. A. Davis Company, 1931. Price, $4.00.

A new chapter has been added on "The Causes of Failure in the Injection Treatment of Varicose Veins," and the chapter on Elephantiasis has been expanded to include the "Elephantoid States Due to Lymphatic Obstruction."

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
W. S. THAYER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Studies on the Relation Between Tumor Susceptibility and Heredity. V. The Influence of Heredity Upon the Incidence of Lung Tumors in Mice.—CLARA J. LYNCH (*J. Exper. Med.*, 1931, **54**, 747) writes that it is well known different constitutional types react in various ways to disease. Particularly interesting is the question of determining whether such types are inherited as the demonstration of inheritance of distinct types may aid in the diagnosis of conditions of nonbacterial origin. The experimental data that have been collected in the author's laboratory concern the incidence of lung tumors in mice are as follows: Strains in mice exist which differ markedly in regard to the incidence of spontaneous lung tumors in the several strains; these strains vary in liability to induced lung tumors and these differences are inherited. It is important to determine whether or not spontaneous tumors in the experiment involved in a cross between strains would parallel those yielded by induced tumors. The experimental work consisted of crossing a male mouse who came from the strain in which there was a high incidence of spontaneous lung tumors with several females from a low-tumor strain. The first generation was then backcrossed to individuals of the original strain. It was found in the backcross from stain D, the high tumor strain, that the incidence of tumor was extremely high, 130 in 204 mice, whereas the backcross from strain 1194, in a total of 218, the incidence was only 16 in the mice that were over 6 months. The more detailed observations cannot be recorded due to lack of space. Suffice it to say that the author shows that from all evidences there are undoubtedly among mice constitutional types which differ in incidence of tumors of the lungs and that these differences are inherited without any apparent influence of sex. She says also that the number of genetic factors involved has not been determined, and there is a possibility of there being such factors to affect tumor age.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Lesions of Isthmus (Pars Interarticularis) of Laminæ of Lumbar Vertebræ.—CHANDLER (*Surg., Gynec. and Obst.*, 1931, **53**, 273) says that solution of bony continuity at the isthmus is a common lesion of the lower lumbar spine. The presence of such a defect can be determined clinically and by the proper interpretation of good roentgenograms of the lumbar spine. The stability and strength of the lumbosacral articulation is impaired by the presence of such defects. The developmental origin of such clefts has been assumed rather than proved. Further study of spines of the fetus and newborn is desirable. Fractures of the isthmus are frequently complicated by spondylolisthesis. Operation in selected cases will restore stability to the lumbosacral juncture.

Nonvenereal Prostatitis.—BRIGGS (*Urol. and Cutan. Rev.*, 1931, **35**, 551) finds that the prostate is not ruled out as a focus of infection as often as it should be. Nonvenereal, nontuberculous prostatitis is insufficiently stressed in most of our standard textbooks. This review has led the author to believe that 18 to 20 per cent of all cases of prostatitis are of nonvenereal origin. A diagnosis of chronic prostatitis often requires several examinations, and in most cases the examination means much more than palpation. The symptoms are very variable. Treatment may or may not be satisfactory, but in most cases requires time and patience.

Carcinoma of the Thyroid Gland.—DUNHILL (*Brit. J. Surg.*, 1931, **19**, 83) says that there are three types of cancer of the thyroid, scirrhus, papilliferous adenocarcinoma and malignant adenoma. In the thyroid gland epithelial proliferation is the characteristic response to stimulation. The proliferation may resolve spontaneously or under treatment. It may form a benign tumor or it may form a tumor which invades and disseminates. These stages merge into one another by insensible gradations. These histologic gradations cause difficulty in deciding just when a tumor has become malignant. Proliferation of thyroid epithelium may be papilliferous or follicular in type. Papilliferous adenocarcinoma may be an ultimate result of the former malignant adenoma of the latter type. A nodule in the thyroid should not be regarded as of no importance, and early changes in signs or symptoms associated with it should induce the practitioner to investigate the cause of these changes. Histologic examination should be made in every case of removal of thyroid tissue, and sections should be made in every case of removal of thyroid tissue, and sections should be taken from different areas. Advanced cases should not be regarded as hopeless when the condition of the patient justifies it, as much of the tumor should be removed as possible and then Roentgen ray treatment commenced. By this means comfort is given and life is sometimes prolonged to a surprising extent.

THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.,
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,
AND
SOMA WEISS, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

Apomorphin in the Treatment of Paroxysmal Tachycardia.— VIKTOR WEISS (*Med. Klin.*, 1931, **27**, 1608) reports most favorable results in the rapid control of paroxysmal tachycardia from the subcutaneous injection of 10 mg. of apomorphin. Favorable results were obtained in this one patient in five different attacks. The author discusses the use of apomorphin for this purpose emphasizing the fact that its potent emetic action is accompanied by powerful vagal stimulation. He cites one other report in the literature of a similar use of apomorphin. In closing he feels justified in recommending this agent both on the basis of its probable effectiveness and upon its safety. Attention is also directed to the fact that emesis induced by other methods has been proved frequently to abate attacks of paroxysmal tachycardia.

The Use of Sulphur in Peripheral Vascular Disease.—Marked benefit often follows the production of fever by the administration of non-specific proteins in patients with chronic peripheral vascular disease. This form of therapy, however, carries with it certain inherent dangers and disadvantages. In the intramuscular injection of sulphur, it also produces fever which is of much longer duration than that produced by most other methods and of which therapeutic use has been made in the treatment of tabes and paresis. WALLER and ALLEN (*Ann. Int. Med.*, 1931, **5**, 478), therefore, tried the injection of sulphur in a series of patients suffering from thromboangiitis obliterans, arteriosclerotic occlusion in the extremities and patients with painful paresthesia. They found that a dose of from 1 to 3.5 cc. of a 2 per cent suspension of sulphur in olive oil was sufficient to produce a significant elevation of body temperature up to 2° C. above normal which generally occurred without severe chill, began gradually 6 or 7 hours after injection and lasted on the average of 2 days. It is seen from this latter figure that the pyrexia is of considerably greater duration than that produced by the proteins. A serious disadvantage, however, from these injections was found in the development of severe local pain at the site of injection. The therapeutic effects were quite as satisfactory as those following the intravenous use of proteins and sometimes considerably more satisfactory. Despite the disadvantages inherent in the severe local pain, the authors believe that the intramuscular injection of sulphur is particularly advantageous in elderly and greatly weakened patients because of its relative freedom from danger.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Blood Pressure in Boys and Girls Before and After Puberty.—RICHEY (*Am. J. Dis. Child.*, 1931, **42**, 1281) as a result of this study found that the average blood pressures of children increase with age, except that the pressures of females tend to decrease after the 16th year. The forms of the pressure curves indicate that factors other than age are active in changing the slope and direction of the curves. Blood pressures of normal children of the same age vary within wide limits. There are also wide fluctuations of the pressures of any child, which may be explained, to some extent, in terms of known influencing factors. Normal blood pressure may be best described as a range. For larger groups of children, the size of the range does not appear to be influenced by sex, age or race. Significant differences exist between the pressures of the two sexes. The average systolic pressures of girls appear to be higher than those of boys for ages from 10 to 13. After 13 years the pressures of boys exceed those of girls, the differences increasing with age. The average diastolic pressures of girls and boys vary only within the limits of unreliability, but from 11 to 16 years the consistently higher absolute values for girls suggest real differences. The average pulse pressures of boys exceed those of girls after the thirteenth birthday, the difference increasing with age. Systolic, diastolic and pulse pressures are intercorrelated at all ages. The correlation coefficients expressing the relation between systolic and diastolic pressures and between systolic and pulse pressures are positive. The correlations between diastolic and pulse pressures are negative at all ages. These relationships have been interpreted to indicate that persons who have systolic pressures above average tend to have both diastolic and pulse pressures above the average, and according to Stocks those with diastolic pressures above average will tend to have pulse pressures below average but not by the same amount, so that the total or systolic pressures will tend to be above the average also. The negative correlations between diastolic and pulse pressures indicate that the higher the diastolic pressure, the less additional force is necessary to maintain circulation. The coefficients of correlation for systolic and diastolic pressures decrease with age, while those for systolic and pulse pressures increase. The relation between systolic and diastolic pressure changes as the higher levels that accompany increased age are attained. Systolic pressure and to a less extent, diastolic pressure are related to physical development. Systolic pressure is correlated with physical development independent of age. The correlation between height and systolic pressure disappears when weight is held constant. The differences of children as to precocity of sex maturation are reflected in the behavior of the blood pressure. Children different as to the precocity of maturing, are different as to anatomic and physiologic development at all ages before the onset of

puberty and, in some ways, for a number of years thereafter. Differences of the blood pressures of children of any given age are probably as pronounced as those in growth in general. In spite of the correlation between pressure and variables of growth, the physical superiority of children who mature early is not in itself sufficient to account for the behavior of the blood pressure.

Vaccine Treatment of Asthma in Childhood.—MITCHELL and COOPER (*Arch. Ped.*, 1931, **48**, 751) comment that it is impossible to draw conclusions from such a report as this, but that their results and a review of the literature seem to indicate that a certain number of children, whose asthmatic attacks are associated with upper respiratory tract infections, are decidedly benefited by the use of vaccines, and in some attacks, which have previously been frequent and severe, cease for months or years after such treatment. Vaccines are helpful sometimes when other methods of treatment have failed. It is not clear whether the vaccine treatment acts by specific desensitization to microörganisms which the patient harbors in his nose and throat and which may be causative of the asthmatic attacks, or whether the mechanism is simply one of nonspecific protein therapy. In their work they have employed vaccines made from those microörganisms obtained from the patient's nose and throat, to which he was sensitive by skin test. It may be necessary to repeat the treatment with freshly prepared vaccines after a period of several months.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Dermatitis Venenata Due to Shoe Leather.—LEWIS (*Arch. Derm. and Syph.*, 1931, **24**, 597) adds another cause to the already overburdened list of agents capable in suceptible subjects of provoking a contact dermatitis; confirming a similar observation by Bloch. The report is timely, however, inasmuch as the present tendency is to consider all inflammatory dermatoses of the feet to be of fungous origin. The 2 patients reported by the author had a dermatitis of the feet which was only relieved by finding a positive patch test with the offending shoe leather and removal of the cause.

Argyll-Robertson Pupils, True and False.—ADIE (*British Med. J.*, 1931, **136**, 3681) introduces his subject by the apparently contradictory statement that the true Argyll-Robertson phenomenon is an infallible sign of syphilis yet pupils that react on accommodation but not to

light (the usual definition of an Argyll-Robertson pupil) are met with in some 20 odd conditions unrelated to syphilis. For a definition, the author reverts to the original paper of Argyll-Robertson in 1869 who described "4 cases of spinal miosis" in which, although the retina was quite sensitive and the pupils contracted at once on accommodation for near objects, there was no response to light and that only slow and partial dilatation occurred on the application of a strong atropine solution. The writer then proceeds to analyze this definition by stating that the typical A. R. pupil is small, not exceeding $2\frac{1}{2}$ mm. in diameter. Typically the A. R. pupil contracts at once and fully, often excessively, on convergence. Thereafter it dilates again promptly. Furthermore, the pupil in question remains the same size indefinitely regardless of the amount of light that enters it; false A. R. pupils often vary in size or dilate when shaded. The author defines the Argyll-Robertson pupil by the statement "small pupils, constant in size, unaltered by light or shade, contracting promptly and fully on convergence, dilating again promptly when the effort to converge is relaxed, and dilating slow and imperfectly to mydriatics. The pupils may be irregular or unequal; the lids may droop or be retracted." The author believes the term "fixed pupil" is an unfortunate one and should be reserved for pupils that react neither to light, direct or consensual, nor on convergence. Even such pupils often react on forcible closure of the lids. Syphilis is merely one of many causes of partially fixed pupils. In partial or recovering lesions of the third nerve, most often traumatic, the pseudo-Argyll-Robertson pupil of Axenfelt may be observed. The chief clinical features are: the condition is often unilateral; pupils vary in size from time to time; pupils never miotic; the reaction to light, though absent to ordinary tests, is not really abolished; the pupil dilates in the dark; the reaction on convergence is peculiar; accommodation, though normal in range, is sometimes slow; and prompt and full dilatation occurs with mydriatics.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Menorrhagia Treated by Pituitary Hormone.—A most interesting report by NOVAK and HURD (*Am. J. Obst. and Gynec.*, 1931, **22**, 501) deals with the treatment of 51 cases of functional uterine hemorrhage by an anterior pituitary luteinizing substance derived from the urine of pregnant women. In 44 of these the treatment was successful in checking the bleeding even though some of the patients were treated with preparations of somewhat uncertain luteinizing potency. Previous efforts at the organotherapy of this condition have been unsuccessful.

Radiotherapy is very undesirable in young women, so that, because of the frequent intractability of functional hemorrhage, many patients have to submit to repeated curettage. The characteristic ovarian finding in these cases is an absence of corpora lutea. The administration of progestin, if this were available, would be a rational plan of treatment. Progestin, the hormone from the corpus luteum of the ovary, is not yet available for human administration, and its effect would be purely substitutional, as it has no effect on the ovaries. The administration of the luteinizing hormone of the anterior pituitary (prolan B) can be expected to be more fundamental in its effects. This substance has been shown by laboratory studies to produce striking luteinization in the ovaries, and the secretion of the lutein cells is progestin, the element lacking in functional uterine hemorrhage. The hormone can be obtained from the urine of pregnant women, although its extraction is as yet somewhat difficult. In 14 of the 51 cases in this series the bleeding ceased after a single injection, and in 12 after two injections. A large proportion of these cases were of the intractable and recurrent type, many having had from one to four or more curettements. In regard to the method of preparation of the hormone used in this work, it may be stated that the urine from pregnant women is concentrated and subjected to precipitation with water-soluble organic solvents, such as alcohol or acetone, thereby removing a large amount of inert material. Though both prolan A and prolan B are present in the resultant material, the dominant action is that of the luteinizing hormone. The rapidity of the effect in many cases makes it seem certain that the immediate effect is not brought about through the production of lutein tissue and progestin by the ovary. They believe that this immediate effect is exerted upon the still unknown bleeding factor which is the immediate cause of the bleeding in functional hemorrhage and which is influenced by far smaller dosage than would be required to produce histologic changes in the ovary. Their experience has convinced them of the value of this treatment in functional hemorrhages and of its even greater future possibilities.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

Intraocular Blastomycosis.—SCHWARTZ (*Arch. Ophthal.*, 1931, **5**, 581) reports a case of metastatic iritis in a patient, aged 38 years, with systemic blastomycosis, in whom the primary lesion was in the lung. coincident with the onset of the iritis a number of superficial abscesses developed. The patient died within about two months. When the

eye was first examined, in addition to the usual signs of iritis, a small nodule resembling a tubercle was present in the lower part of the iris. This nodule increased in size gradually, became purulent and ruptured into the anterior chamber which became filled with pus. Blastomycetes were recovered from this pus. At the onset of the iritis the fundus was normal. Histologic examination of the eye removed at autopsy showed a purulent keratitis and iritis with numerous blastomycetes. An incision had been made through the cornea for evacuation of the pus in the anterior chamber and apparently the corneal involvement was secondary to this. The ciliary body and choroid were essentially normal. Blastomycosis of the eyelids is frequent in association with other skin lesions. The conjunctiva is almost immune. Corneal ulcers have been reported which probably became infected with blastomycetes from lesions on the lids. Two cases have been reported in which blastomycetes were recovered from purulent intraocular exudation. In both of these the infection was probably through a corneal lesion. No definite case of metastatic intraocular blastomycosis has been reported previously. In the discussion of this paper Kronfeld stated that Stock had obtained tubercle-like lesions in the iris and metastatic retinochoroiditis following intravenous injection of blastomycetes into rabbits.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

The Value of Roentgenography in the Diagnosis of Congenital Syphilis.—Material reviewed in this study by Vogt (*Am. J. Roent. and Rad. Therap.*, 1931, **26**, 96) consisted of 109 infants under 2 years of age and mostly under 1 year. Blood Wassermann reactions were recorded in 91 and found positive in 83, or 91.2 per cent. Eight were negative or doubtful. The roentgenologic examination revealed bone lesions in 95 cases or 91.3 per cent, and in 71.1 per cent the bone changes were definitely diagnostic. The changes readily recognized and of chief diagnostic importance were: (*a*) Bone production exhibited as subperiosteal thickening; (*b*) bone destruction or osteomyelitis, and (*c*) disturbance of growth. Subperiosteal thickening was most common. It must be distinguished from periostitis due to other infections, particularly tuberculosis, and from the pseudoperiostitis seen in rickets. Dactylitis, which is really a periostitis of the phalanges, was noted in 16 cases. Osteomyelitis, evidenced by bone absorption and usually accompanied by new bone formation, was found in 63 per cent of cases. Usually it occurs at or near the ends of the long bones. A special type of osteomyelitis appears as bilateral semilunar defects at the upper ends

of the tibiæ medially, adjacent to or just below the epiphyseal lines; Vogt regards it as pathognomonic of lues. Growth disturbance may be manifested by a dense narrow line at the ends of the diaphyses, with a parallel zone of diminished density.

Gall Stone Obstruction of the Duodenum.—A case in which the duodenum was completely obstructed by a large gall stone is reported by CRANE (*Am. J. Roent. and Rad. Therap.*, 1931, **26**, 92). The shadow of the barium mixture ended abruptly just anterior to the duodenojejunal flexure, and the entire duodenum was dilated. In addition, the opaque mixture entered and depicted the common duct, some of the hepatic ducts, the cystic duct and the gall bladder. On reviewing the literature of the last 8 years, the author found 4 other cases of duodenal obstruction by gall stones, and 26 of similar obstruction in the small bowel beyond the duodenum.

Irradiation Treatment of Myoma of the Uterus.—Two hundred and eighty-four cases of uterine myoma were treated by SCHREINER (*Radiol.*, 1931, **17**, 265). The size of the tumor was definitely influenced in 85 per cent, with regression to normal or at least a diminution to half the original size. Bleeding was controlled in from 96 to 100 per cent. Of the cases treated 98.5 per cent became symptomatically well. The menopausal symptoms—neurosis, hot flashes, sweating—with few exceptions did not seem to be any more severe after irradiation than in the average menopause.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Deafness in Trichinosis.—BOSCH (*München. med. Wchnschr.*, 1931, **78**, 436) reports the case of a female, aged 51 years, who was admitted to a hospital with a trichina infection, 23 days after ingestion of ham from bears. Her symptoms comprised drowsiness, pains in the muscles and stiffness; blood examinations revealed an eosinophilia and demonstrated the trichinæ. Two weeks after eating the bear flesh she first noticed deafness. Ten days after admission she was totally deaf; air and bone conduction were both lost; it was impossible to carry out the Weber or Schwabach tests. No abnormality could be detected in the ear passages or tympanum; the nose and throat were also healthy. A complete otologic examination was carried out every 3 days and a slow improvement became evident. After she had been in the hospital about a month, she was able to understand vowels and syllables shouted directly into her ear. The author regards the deafness as due to toxic acoustic neuritis rather than to a direct implication of the eighth nerve by the trichinæ.

The Glucose Tolerance Curve in Epilepsy.—MACKAY and BARBASH (*J. of Mental Science*, 1931, **72**, 83) state that while there is no typical glucose tolerance curve in epilepsy, a high percentage of epileptic patients present a glucose tolerance curve of a definitely subnormal type. The writers have attempted to correlate the type of epileptic (viz., irritable, confused, demented) with the blood-sugar level, but have been unable to determine that there is any such relation. Similarly they have been unable to establish any definite relation between frequency of fits and the blood-sugar level. The comparatively high percentage of cases with renal glycosuria in their series is worthy of note.

Curable Forms of Purulent Meningitis of Traumatic Origin.—BREGMAN and KRUKOWSKI (*L'Encephale*, 1931, **26**, 110) find that meningitis is one of the most fatal complications of fracture of the skull. They present, however, 3 cases which recovered. In the first case, coliform bacilli were found in the cerebrospinal fluid, in the second case hemolytic streptococci, while in the third the fluid, although purulent, remained sterile. In the first and third cases a fixation abscess produced by an injection of turpentine appeared to have a beneficial effect.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
W. L. HOLMAN, M.D.,
PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Protective Measures of the State of California Against Botulism.—In a Cutter Lecture delivered by Harvard Medical School MEYER (*J. Prev. Med.*, 1931, **5**, 261) summed up the developments preceding the organization of scientifically controlled canning procedures and their effect on the incidence of botulism in the United States. He states that food commercially preserved in the United States has not been connected with any of the recognized cases of botulism since 1925, therefore the processes of canning should be under official supervision in every state of the Union. In the 193 single and group cases of botulism occurring over a period of approximately 30 years 131, or 68 per cent, with an average mortality of 65 per cent, were caused by home-canned or home-preserved food articles, usually vegetables. Understerilization or inadequate curing have with monotonous regularity been the prime factors. To prevent the occurrence of tragedies due to poisonous string beans or corn is one of the pressing problems. Irrespective of the fact that botulism is one of the few diseases which can be readily avoided, groups of people continue to ignore the two following simple rules: (1) All home-canned vegetables and other nonacid foods should be thoroughly boiled before use. (2) The person who opens the container and prepares the contents for the table should be familiar with the standards of quality and should ruthlessly discard

any product which has leaky lids, an "off odor" or other signs of spoilage. Public health workers have been led to advocate the preservation of nonacid foods by drying, by curing in 10 per cent brine or by pickling in acidified brine. Aside from being simple and inexpensive, these methods have the one great advantage that the food is "not ready to be served" from the jar, but requires thorough soaking in water and sometimes subsequent boiling—the greatest safety device against botulism. Until there is an end to the custom of serving home-canned string beans and other vegetables cold as salads, often heavily seasoned with vinegar or mayonnaise dressings, which disguise any suspicious odors, botulinum intoxications may be anticipated. Every farmer's wife feels qualified to preserve vegetables in a glass jar. Spoilage is frequently so slight that even a competent observer may be misled. Moreover, the unboiled contents of many jars may have been consumed without bad effects, and thus a false confidence leads finally to the disastrous meal. Neither laws similar in character to that promulgated by Emperor Lex, in 905, for the purpose of preventing botulism due to blood sausages, nor official supervision, which is obviously impossible, but only the education of the masses as to the necessity for boiling all home-canned vegetables before use will in time prevent the frequent and needless deaths from these products.

Hepatitis by Streptococci.—McMahon and Mallory (*Am. J. Path.*, 1931, **3**, 299) studied the pathologic changes in 5 clinical cases of streptococcic hepatitis. In 3 of these clinical cases the organism was demonstrated in the tissue, while in the other 2 the infectious genesis was assumed because of the lesions found. Five representative types of reactions are described: (1) Necrosis of liver cells particularly of the intermediate zones but spreading to involve the whole lobe with endothelial cell infiltration but no abscess formation. (2) Extensive focal necrosis of liver cells with endothelial cell infiltration, the mass of the liver, however, remaining normal. (3) Lesions uniformly distributed throughout the organ consisting of a zonal degeneration involving the periphery of the lobules but not those cells immediate to the portal areas. (4) Great proliferation of the bile ducts with atypical cells and increase in the interstitial tissue with the original lobular architecture displaced. (5) Minute grayish areas made up of numerous bile ducts but devoid of liver cells, while the portal vessels were still present. A pure culture of Streptococcus hemolyticus which had been isolated from a patient with scarlet fever was used for animal experiments. An injection was made into the mesenteric vein of rabbits with aseptic technique. These all had positive blood cultures after 12 hours. One rabbit died in 18 hours with numerous streptococci in the liver. Another dying in 24 hours showed fewer bacteria, while in one killed after 48 hours very few streptococci were to be found and in the animal killed after 5 days no organisms were to be found and very little evidence of damage. All showed however, some degree of focal necrosis, which was not limited to the central vein areas thus differing from chemical and bacterial toxemias. The authors would not attribute an infectious origin to all liver cirrhoses but they emphasized the similarity of the lesions resulting from streptococcic infections to that of the healed stages of acute yellow atrophy, and suggest that in many cases of the latter sufficient search might reveal a possible streptococcus etiology.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

The Germicidal and Therapeutic Applications of Soaps.—WALKER (*J. Am. Med. Assn.*, 1931, **97**, 19) states that soaps are strongly bactericidal against pneumococci, streptococci, meningococci, gonococci, diphtheria bacilli, influenza bacilli and Spirochæta pallida. Their activity against these organisms compares favorably with that of many of the recently synthesized chemicals. When properly used for cleaning the hands or for the washing of eating utensils soaps are undoubtedly potent factors in preventing the spread of diseases due to these organisms. The action of soaps as germicides is, however, limited by the fact that they do not destroy staphylococci and typhoid bacilli. Renaud has recently found 2 per cent solutions of sodium oleate beneficial as an irrigation and wet dressing for ulcerated surfaces.

The Epidemic of So-called Ginger Paralysis in Southern California in 1930–1931. SMITH and ELVOVE (*U. S. Pub. Health Rep.*, 1931, **46**, 1227) have had occasion to study an outbreak of paralysis due to the use of illicit ginger extract as a beverage. They report that in spite of the wide publicity given to this form of poisoning, a year ago this new outbreak occurred in California, also a smaller one in Massachusetts. The outbreak referred to consisted of about 125 cases, and in every case there was a history of the use of Jamaica ginger extract bought from drug stores. Chemical tests showed the presence in each offending sample of the phosphoric ester of orthocresol, which chemical had been found in the earlier outbreak and accounts for the symptoms. Details of the chemical and pharmacologic studies are given, and the opinion is expressed that future outbreaks of the poisoning may be expected unless effective steps are taken to prevent the distribution of the toxic material.

Studies on Meningococci Isolated in the United States, 1928–1930 Serologic Classification and Geographic Distribution. BRANHAM, TAFT and CARLIN (*U. S. Pub. Health Rep.*, 1930, **46**, 897) note the disappointing results of serum therapy in epidemic cerebrospinal meningitis in recent years and have studied types of meningococci prevalent in the later epidemics. About half the strains were well agglutinated by the commercial serums used, and most of the remainder of the strains were agglutinated by these serums in some degree. It is not implied that the agglutinability indicates therapeutic efficiency of the serums against this specific organism. More than 80 per cent of the strains recently

isolated fell into a group which includes the Groups I and III. The authors report that while small isolated outbreaks are often due to one type of meningococci, more extensive outbreaks may involve all varieties.

The Smallpox (Alastrim) Epidemic in Holland.—JITTA (*U. S. Pub. Health Rep.*, 1930, **45**, 66) reports that a sailor arrived at Rotterdam ill, infected his wife and she in turn infected the only unvaccinated child in the family (4 children). There was an outbreak of 8 cases in a hospital. Much question existed as to the diagnosis for a time, and it was finally reported as "alastrim." The death rate in Rotterdam was 5.5 per cent but *nil* in the remainder of the country. Following the extensive vaccination there was an outbreak of postvaccinal encephalitis—168 cases with 14 deaths.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 11, 1932

The Effect of Amebicidal Drugs on Tissue Culture Cells.—MARY JANE HOGUE (from the Laboratory of Anatomy, University of Pennsylvania). Much work has been done on the effect of certain drugs on Entamœba histolytica but little is known of the effect of these drugs on the tissues of the host. There are three drugs generally used in the treatment of infections of Entamœba histolytica: emetin hydrochlorid, yatren (iodoxyquinolin sulphonic acid), and dihydranol (2 to 4 dihydroxy phenol-n-heptane). A fourth substance is being used by Dr. de Rivas. It consists of equal parts of glycerin and a 30 per cent solution of magnesium sulphate. These four amebicidal drugs were made up with Locke-Lewis solution in dilutions of 1 to 1000, 1 to 10,000 and 1 to 50,000. Emetine was also diluted 1 to 100,000.

Tissue cultures were made from small pieces of the intestine of embryonic chicks 7 to 9 days old. They were grown in hanging drops in Locke-Lewis solution for 2 to 3 days or until there were good growths of epithelium, mesothelium, nerves and fibroblasts. The Locke-Lewis solution was then withdrawn and the tissue culture was completely covered with a loop full of one of the diluted drugs. The effect of the four drugs in their various dilutions was then studied microscopically in a warm box.

It was found that dihydranol diluted 1 to 1000 kills the cells at once *in situ*. In the higher dilutions it injures the cells at first. Later the tissues adjust themselves to the new medium and form fairly normal growths.

Emetine hydrochlorid in all the dilutions used kills the tissue culture cells. They disintegrate and the hanging drop is a mass of débris.

Yatren diluted 1 to 1000 kills the tissue culture cells slowly. In the higher dilutions there is slight injury at first followed by fairly normal growths.

The de Rivas mixture of glycerin and magnesium sulphate is slightly toxic to the tissue culture cells in the dilution 1 to 1000 but they soon adjust themselves to the solution and normal growth follows. The higher dilutions do not affect the growth though at first there is a slight shrinking of the outermost cells.

A Study of the Gregory and Pascoe Modification of the Pettenkofer Reaction and Its Application to the Determination of Bile Acids in Bile.—JOHN REINHOLD and D. WRIGHT WILSON (from the Biochemical Laboratory of the Philadelphia General Hospital and the Laboratory of Physiological Chemistry, University of Pennsylvania). The technique described by Gregory and Pascoe[1] does not yield the greatest possible amount of color obtainable from the cholic acids. An experimental study of the reaction between cholic acid, furfural, and H_2SO_4 was made in order to find the most favorable conditions, which proved to be the following: 12 NH_2SO_4, 10.4 mg. furfural, 0.05 to 0.3 mg. cholic acid in a total volume of 8 cc. heated in 18-mm. tubes at 70° C. for 8 minutes. The solution was cooled 2 minutes and read colorimetrically against a standard containing 0.215 mg. sodium cholate in red light of about 6100 to 7000 Å. For the analysis of human bile the protein must be removed by precipitation with alcohol and heat. This is not necessary when dog bile is the material.

A spectrophotometric study of the blue color formed in the reaction showed a well-defined absorption band with a peak near 6700 Å. By the modified technique the light absorption was about twice as great as by the Gregory and Pascoe procedure. An attempt was made to obtain additional information concerning the interfering effect of other substances that might be present by heating dog bile with 12 NH_2SO_4 alone in the absence of furfural. Absorption spectra of solutions so treated indicate that some of the blue derivative of cholic acid is formed even in the absence of furfural, but that the absorption of bile heated under these conditions decreases rapidly from 6100 Å. upward, indicating that the filters should cut off light below this wave length. The effect of biliverdin cannot be eliminated by filters, but interference from this source is not significant if precautions are taken to check the oxidation of bilirubin.

Conjugated and unconjugated cholic acids give equimolar quantities of color. Through the kindness of Dr. Carl H. Greene of the Mayo Clinic, we were able to compare the acetic derivative of sodium desoxycholate with the color produced by cholic acid under the conditions of the modified method. The purest sample of sodium desoxycholate gave only slightly more color than the reagents alone, a second gave $\frac{1}{14}$ and a third gave $\frac{1}{7}$ of the amount of color yielded by an equimolar amount of cholic acid. It seems reasonable to conclude, therefore, that the color was due to impurities, perhaps cholic acid incompletely removed, and that the method is specific for the cholic acid series.

Induction of the Ear from Foreign Ectoderm in the Embryo of Amblystoma Punctatum.—C. L. YNTEMA (from the Laboratory of Anatomy, Yale University). The potency of ectoderm outside the ear region to form an ear was studied experimentally in the embryo of Amblystoma

[1] Gregory, R., and Pascoe, T. A.: J. Biol. Chem., 1929, **83**, 35.

punctatum. Ectoderm from posterior to the ear rudiment, when transplanted to the ear region during the later neural plate stage, frequently formed functional labyrinths. In the early head process stage, power to form an ear from this ectoderm was lost. In experiments performed between these stages, labyrinths of intermediate normality developed.

The relative potency of different regions of foreign ectoderm to form an ear was determined by transplanting ectoderm from several different parts of the embryo into the ear region when the neural folds were approximating. The ectoderm from the region ventral to that of the ear was more labile than transplants from any of the other regions.

Experimental Studies in Gastric Physiology in Man: An Evaluation of the Rôle of Duodenal Regurgitation in the Control of Gastric Acidity (Boldyreff Theory).—Harry Shay, Albert B. Katz and Eugene M. Schloss (from the Gastro-intestinal Clinic of the Jewish Hospital, Philadelphia). Since Heidenhain's observation that the pure gastric juice in the normal dog was secreted at an acidity of 0.5 to 0.6 per cent hydrochloric acid and particularly since its confirmation in human beings by Carlson, physiologists have puzzled over the mechanism involved in the reduction of this high acidity to the one ordinarily seen in gastric contents. Of the theories evolved to explain this reduction, that of Boldyreff has enjoyed the greatest popularity. Briefly this theory contends that the relatively strong gastric acid (0.5 per cent) entering the duodenum provokes an abundant secretion chiefly of pancreatic juice. At the same time the acid through its irritant action on the duodenal mucosa, causes antiperistalsis in the duodenum, which in turn carries back into the stomach the alkaline pancreatic juice. This regurgitated juice in the stomach reduces the gastric acidity to approximately 0.15 per cent at which concentration it may be tolerated by the duodenum.

We studied this mechanism in human beings, using as a measure of regurgitation the amount of bromsulphalein present in the gastric contents, after the intravenous injection of the dye.

Bromsulphalein when introduced into the blood stream is taken out almost quantitatively by the normal liver. From the liver it finds its way to the second portion of the duodenum by way of the bile. The dose of dye used throughout the studies was 5 mg. per kilo body weight. The patients selected represented the entire range of gastric acidity as determined by Ewald meal and by histamin. More than 60 determinations were made.

Before making these determinations with various test substances, all patients were first standardized: (1) For removal of dye by the liver (blood estimation); (2) for regularity of appearance time of the dye in the duodenum through duodenal tube; (3) for the concentration of the dye in the duodenal contents during 20-minute periods for 2 hours after the duodenal appearance of the dye; (4) for the elimination of the dye by the kidneys during the test period.

The above determinations were repeated three times on each patient.

Following this standardization the fasting stomach was intubated. After emptying the stomach in all positions, the proper amount of dye was injected intravenously. At the duodenal appearance time for the particular patient the stomach was again emptied in all positions. Following this the patient ingested the test meal. This consisted, on suc-

cessive days, of 200 cc. of tap water, 200 cc. of 0.2 per cent and 0.5 per cent hydrochloric acid, and of 1 and 5 per cent sodium bicarbonate. Five minutes after the test meal was taken, the stomach was again emptied in all positions. The amount recovered was mixed and measured. It was then returned to the stomach through the tube by gravity, excepting 15 cc., which was retained. Subsequently at 20-minute intervals for 2 hours, the procedure, as at the 5-minute interval, was repeated. Each specimen retained was then titrated for free and total acidity and for the amount of dye when present. Knowing the approximate concentration of the dye in the duodenum at the corresponding times, measuring the amount of gastric contents and determining the concentration of dye when present in the mixed specimen, enabled us to form a very definite idea of the amount of regurgitation that must have taken place.

While we do admit that duodenal regurgitation into the stomach may and does frequently take place, we cannot, from our experiments, ascribe any importance to this mechanism in the regulation of gastric acidity. The results of our experiments are in agreement with McCann, that the control of gastric acidity depends essentially upon some intragastric mechanism. Our experiments also suggest the possibility of acid absorption in the stomach. Experimental data is presented indicating the fallacy of dissociated regurgitation of the bile and pancreatic juice from the duodenum into the stomach.

Corrections

In the article by Mora and Greene on "Thyroidectomy for Thyrotoxicosis in Older People" in the January, 1931, number of this Journal the paragraph preceding the Summary on page 80 which now reads "One death occurred in the remaining 860 cases which comprised this series. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66 per cent" should read "Three deaths occurred in the remaining 860 cases which comprised this series. The total mortality (9 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.84 per cent." A similar correction should be made in paragraph 11 of the Summary.

In the Progress notes for Therapeutics in the February, 1932, number of this Journal, the reference to the article by Winternitz on page 282 should be "Ztschr. f. Kreislaufforsch., 1931, **23**, 452."

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